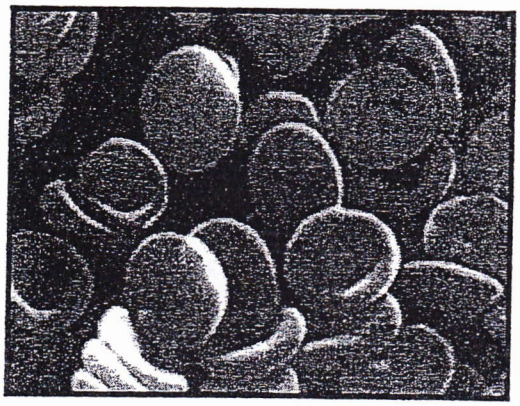

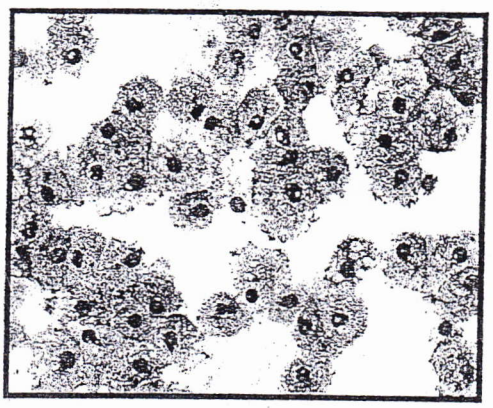

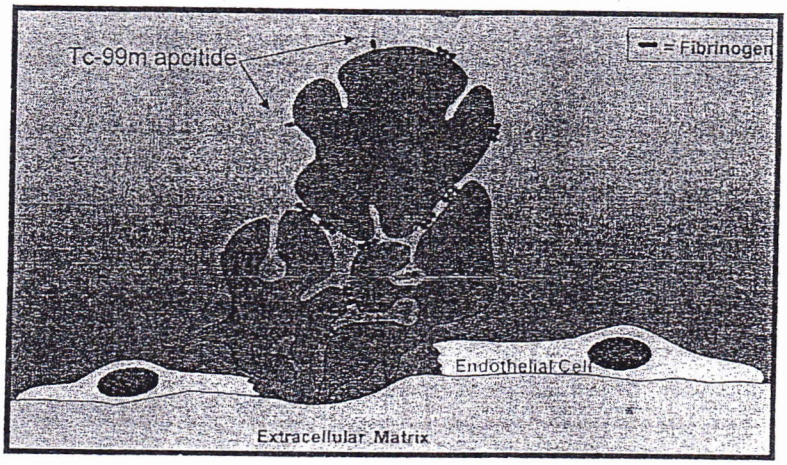

Pediatric Hematology

By

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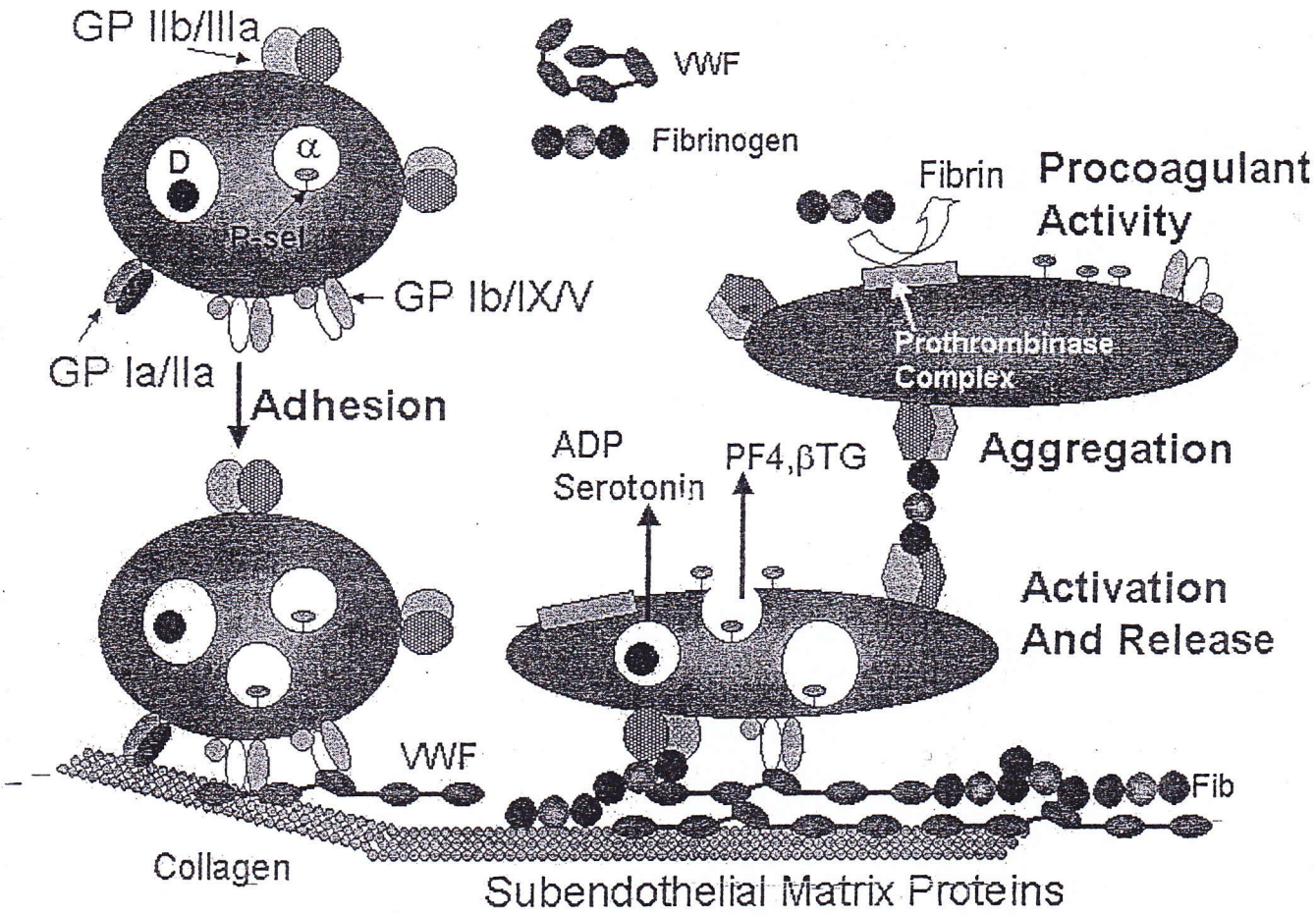
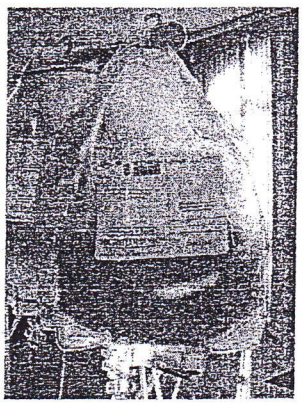
2009

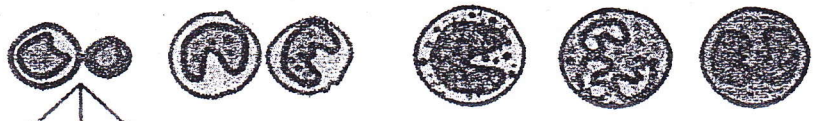




Leukocytes

white blood cells ~ WBC

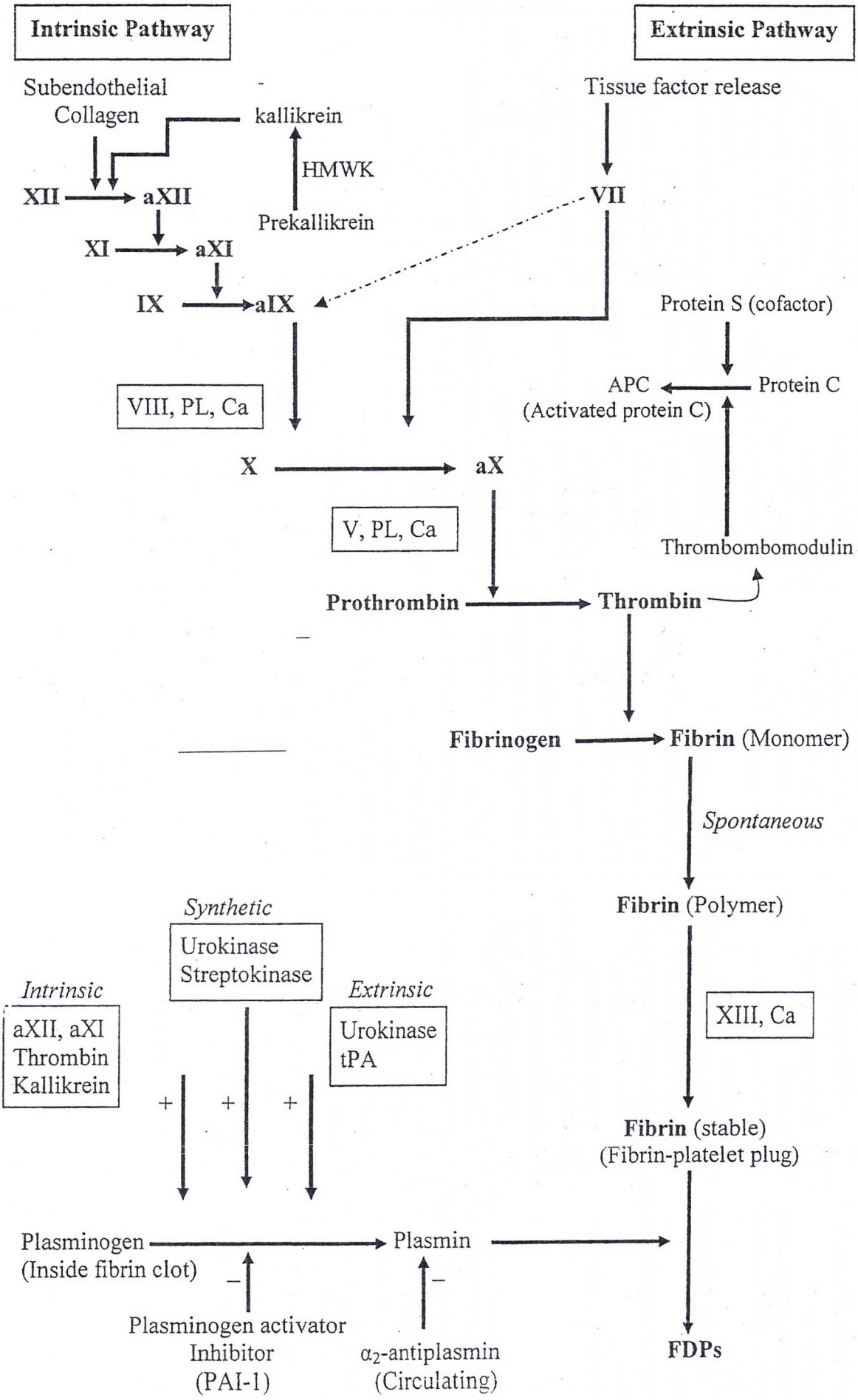
agranular		granular		
lymphocytes 20 - 25 %	monocytes 3 - 8%	basophils .5 - 1%	neutrophils 60 - 70%	eosinophils 2 - 4%



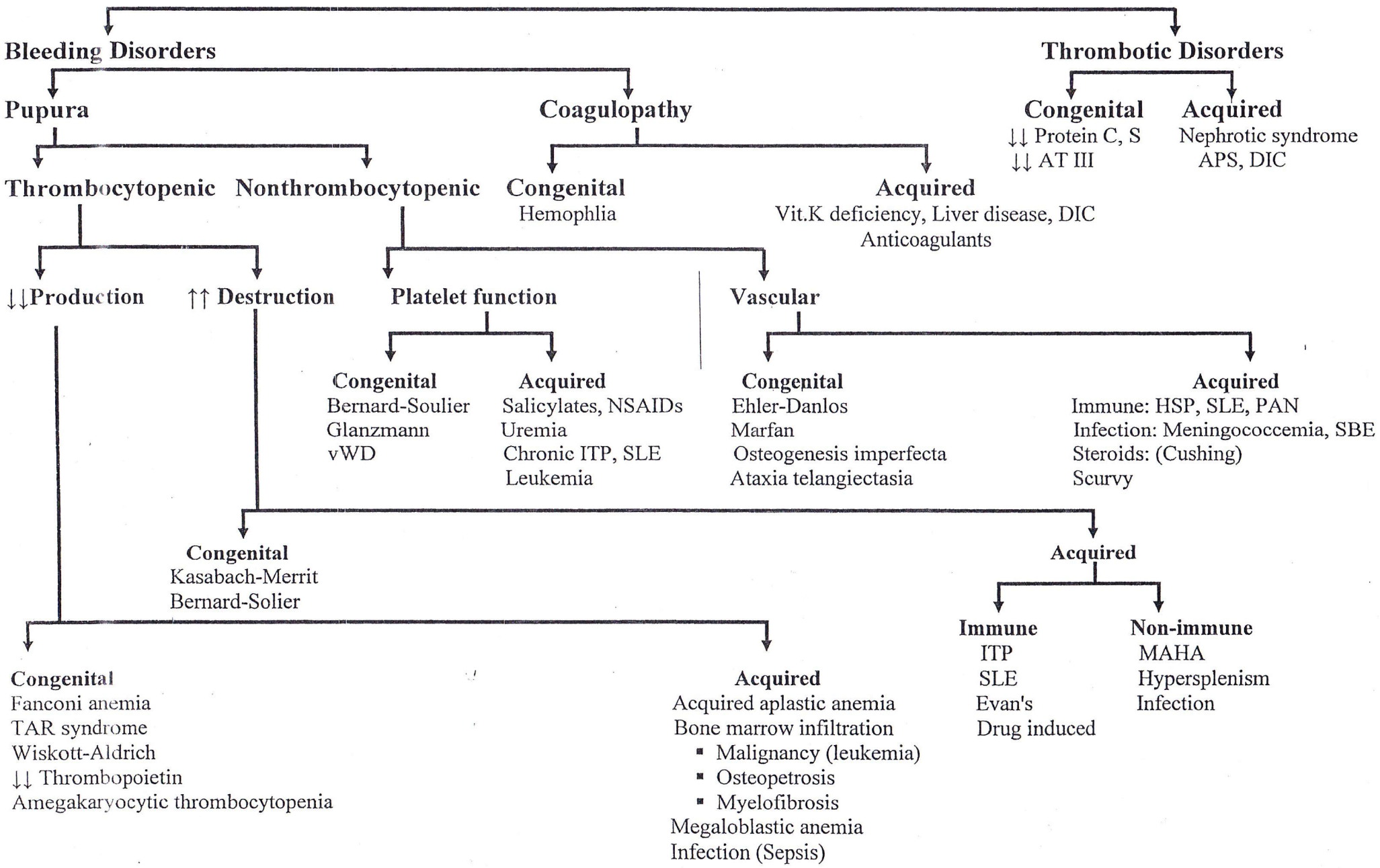
T-cell, B-cell, NK Cell

Hemostasis

	Vascular	Platelet	Plasma factors: Coagulation	Plasma factors: Fibrinolysis (Plasmin)	Natural anticoagulants
Function	**1. VC** ▪ Reflex ▪ Serotonin (Platelet) **2. Exposure of subendothelial matrix** ▪ ↑↑ vWF (Plt adhesion) ▪ ↑↑ XII (↑↑ Intrinsic pathway) **3. Release** of Tissue thromboplastin → ↑↑ VII (↑↑ Extrinsic pathway)	**1. Adhesion** to subendothelial matrix (vWF mediated) **2. Aggregation** By ▪ ADP ▪ Thromboxane A_2 **3. Release** ▪ Serotonin (VC) & TXA_2 ▪ ADP (aggregation) ▪ Phospholipids (PL) ▪ Thrombosthenin → (clot retraction) **4. Platelet plug formation** **5. Stabilization** of fibrin platelet plug by XIII	**1. Phase I** (formation of prothrombinase) ▪ Intrinsic pathway XII, XI, IX, VIII, X, V ▪ Extrinsic pathway Tissue thromboplastin, VII X,V **2. Phase II** Prothrombin → Thrombin **3. Phase III** Fibrinogen → Fibrin monomer → Polymer **4. Phase IV** (Stabilization of fibrin polymer by XIII)	Essential mechanism: ▪ # Extension of the clot ▪ BV patency **1. Activators** ▪ Intrinsic: aXII, aXI, Kallikrein, Thrombin ▪ Extrinsic: Urokinase, tPA (tissue plasminogen activator) ▪ Synthetic: Urokinase, Streptokinase **2. Inhibitors** ▪ Plasminogen activator inhibitor (PAI-1) ▪ α_2 antiplasmin	**1. Protein C** Activated by thrombin-thrombomodulin complex → APC → Inactivates aV, aVIII *(Thrombomodulin is present on the intact endothelial surface)* **2. Protein S** Cofactor for protein C **3. Antithrombin III** # Thrombin, X,IX,XI,XII **4. Tissue factor pathway Inhibitor (TFPI)** ↓↓ activation of X by VII
How to test	**1. Hess test** (Tourniquet test) (N = <5 petechiae in 2.5 cm^2) ▪ Blood vessel ▪ Platelet(No&function) **2. Bleeding time** (4-8 min) ▪ Blood vessel ▪ Platelet (No & function) **3. Platelet No.** Platelets are essential for BV integrity	**1. Platelet count** (150.000-400.000/ mm^3) Patients with count >50.000 rarely have significant bleeding **2. Bleeding time** **3. Platelet function** ▪ Adhesion ▪ Aggregation (ristocetin, collagen, ADP) ▪ Clot retraction ▪ vWF (Ag & activity)	**1. Phase IV** 5M urea test (soluble clot) **2. Phase III** Fibrinogen assay Thrombin & Reptilase time (N = 11-15 sec) **3. Phase I, II** Specific factors PT (10-13 sec) = VII, X, V, II PTT (25-40 sec) = XII, XI, IX, VIII, X, V, II Corrected by plasma = VIII Corrected by serum = IX Corrected by Both = XI Not corrected = XII **4. Coagulation time** (8-12)	**1. Euglobulin clot lysis time (ELT):** (N = 2-4 hrs) Short ELT: ▪ ↑↑ Plasminogen activators ▪ ↓↓ Fibrinogen Prolonged ELT: ▪ ↓↓ Plsminogen ▪ ↓↓ Plasminogen activators ▪ ↑↑ Fibrinogen **2. Plasminogen** **3. Plasminogen activators & inhibitors** **4. Fibrin degradation products (FDPs)**	**1. Measurement of** ▪ Protein C ▪ Protein S ▪ Antithrombin III


Intrinsic Pathway
Extrinsic Pathway
Subendothelial Collagen
kallikrein
HMWK
Prekallikrein
XII
aXII
XI
aXI
IX
aIX
Tissue factor release
VII
Protein S (cofactor)
APC (Activated protein C)
Protein C
VIII, PL, Ca
X
aX
V, PL, Ca
Thrombombomodulin
Prothrombin
Thrombin
Fibrinogen
Fibrin (Monomer)
Spontaneous
Fibrin (Polymer)
Synthetic
Urokinase
Streptokinase
Intrinsic
aXII, aXI
Thrombin
Kallikrein
Extrinsic
Urokinase
tPA
XIII, Ca
Fibrin (stable)
(Fibrin-platelet plug)
Plasminogen
(Inside fibrin clot)
Plasmin
Plasminogen activator
Inhibitor
(PAI-1)
α2-antiplasmin
(Circulating)
FDPs

Coagulation Disorders



Bleeding Disorders

Classification

a. Purpura **b.** Coagulopathy

General Features

	Purpura	Coagulation disorders
Defect	Platelet or vessel wall	Coagulation factors
Skin lesions	Petechiae 1-2 mm Ecchymosis 1-2 cm	Ecchymosis
Site of bleeding	Mucous membranes (mouth, gums, epistaxis, conjunctiva) Internal Hge (ICH) less common	Deep bleeding; joints (hemoarthrosis), muscle (hematoma)
Relation to trauma	Immediate Usually spontaneous	Usually delayed (oozing) Usually traumatic

Coagulation Disorders

Classification

a. Inherited: Hemophilia (A,B.C), vWD & other coagulation factor deficiencies

b. Acquired: vitamin K deficiency, advanced liver disease, DIC, anticoagulants & acquired inhibitors of coagulation (APS, following Rx with F VIII or IX)

Hemophilia A (Classic hemophilia)

Definition

It is the commonest cause of hemophilia (85%). **Incidence** = 1: 5000 ♂

Genetics& Etiology

- X-linked recessive (Its locus is close to that of G-6-PD & color blindness)
- Some female carriers of hemophilia may have mild bleeding (lyon hypothesis)
- 20% of cases are new mutations
- The hemostatic level of factor VIII is > 30-40 U/dL
- ↓↓ Factor VIII (intrinsic pathway). According to plasma level of factor VIII:

Factor VIII	Severity	Bleeding tendency
< 1 %	Severe	Spontaneous- Joint/muscle bleeding
1-5 %	Moderate	Bleeding after minor trauma
> 5-30	Mild	Bleeding after surgery

Clinical picture

- Bleeding tendency may be evident in the neonatal period
- Post circumcision bleeding
- Easy bruising
- Unusual hematomas (muscle hematoma → fibrosis → contracture → deformity)
- Hemartrosis is common (Pain, tenderness, swelling, flexion, tense overlying skin)
- Hematuria, epistaxis, bleeding gums, post-tooth extraction bleeding, ICH

Investigations

- Coagulation time & PTT: ↑↑ (corrected by plasma)
- Factor VIII assay: ↓↓
- PT, TT, Bleeding time, platelet count: normal
- Prenatal diagnosis: Factor VIII assay in fetal blood (fetoscopy) & DNA study

Treatment

Avoid
- Trauma
- IM injection
- Deep veins
- NSAIDs

A) General measures
- Careful observation & psychological support
- Avoid trauma, salicylates & NSAIDs
- Avoid IM injection, deep veins for venipuncture (use superficial veins)
- HBV vaccine
- Hospitalization: head trauma, neck swelling & marked hemarthrosis

B) Prophylactic therapy
- Factor VIII prophylactic therapy : in **severe** cases to prevent spontaneous joint bleeding
  It is given every 2-3 days (IV) to maintain factor VIII trough level 1-2 U/dL

C) Management of bleeding (Half life of factor VIII= 12 hours)

a. Recombinant factor VIII: supplied as powder (Recombinant DNA technology)
Dose of factor VIII = 0.5 **X** BW **X** [% desired ↑↑ in plasma F VIII] ≈ 20-40 U/Kg

b. Lyophilized concentrate (freeze-dry): supplied as powder prepared from many donors (↑↑ risk of HIV& HBV transmission)

c. Cryoprecipitate: fraction of 1 Unit frozen plasma *(It contains VIII, vWF, I, XIII)*

d. Fresh frozen plasma: 10-15 ml/Kg/12 hours

e. Desmopressin (0.3 µg/Kg IV or 150-300 µg intranasal): in **mild** cases (It ↑↑ endogenous factor VIII)

f. Antifibrinolytic therapy in mucosal bleeding (epistaxis, mouth, dental…)

- ☒ Prednisone may be given in hemarthrosis & persistent hematuria
- ☒ Joint aspiration may be indicated in hip hemarthrosis to prevent avascular necrosis
- ☒ Antifibrinolytic therapy is contraindicated in hemarthrosis & hematuria
- ☒ Continuous infusion is needed in life threatening conditions & major surgeries

Complications

a. Chronic joint destruction and muscle atrophy & contracture

b. Death (ICH, massive bleeding…)

c. Complications of therapy:

☒ Development of inhibitors (Ab): ↓↓ response to appropriate replacement therapy

Rx: **a.** ***Continue*** on regular dose (spontaneous Ab loss)
b. ↑↑ ***dose*** to induce tolerance
c. ***Recombinant*** FVII or prothrombin complex concentrate to bypass the defect

☒ Transmission of blood born diseases (HIV, HBV, HCV, Parvovirus…)

☒ Allergy, anaphylaxis, renal disease (immune complex disease)

Hemophilia B & C

	Hemophilia B	Hemophilia C
Defect	F IX ↓↓ **(Christmas disease)**	F XI ↓↓
Half life	24 hrs	48 hrs
Incidence	10-15 %	2-3 %
Inheritance	X-linked recessive	Autosomal Recessive
C/P	As hemophilia A	Milder or No bleeding
Lab	F IX assay ↑↑ PTT (corrected by serum)	F IX assay, ↑↑ PTT (corrected by plasma & serum)
Treatment	F IX (Recombinant / lyophilized), FFP	FFP
	Desmopressin & Cryoprecipitate are **ineffective**	

Other Coagulation Factor Deficiencies

	Defect	C/P	Lab	Treatment
Factor XII Deficiency	↓↓ F XII (Hageman F)	**No bleeding** ± may thrombosis (↓↓ plasminogen)	↑↑ PTT (Not corrected by plasma or serum), F XII	**No** Rx is needed
Von Willebrand San Diego $	↓↓ F XII + ↓↓ vWF	Mucocutaneous Bleeding	↑↑ PTT	As vWD
Deficiency of contact factors	↓↓XII,HMWK ↓↓Prekallikrien	**No bleeding**	↑↑ PTT	**No** Rx is needed
Factor V Deficiency (Owren disease)	↓↓ F V Parahemophilia (Labile factor)	Mucocutaneous bleeding, Hemarthrosis (rare)	↑↑ PTT ↑↑ PT F V assay	FFP
Combined Factor V&VIII Deficiency	↓↓ F V ↓↓ F VIII	Mucocutaneous bleeding Hemarthrosis (rare)	↑↑ PTT ↑↑ PT FV,VIII assay	As ↓↓ FVIII
Factor VII Deficiency	↓↓ F VII (Stable factor)	Mucocutaneous bleeding, **spontaneous ICH**	↑↑ PT F VII assay	FFP ($T_{1/2}$ =2-4 hr) Recombinant FVII
Factor X Deficiency	↓↓ F X (Stuart-Prower)	Mucocutaneous bleeding	↑↑ PTT ↑↑ PT F X assay	FFP ($T_{1/2}$ =30 hrs)
Factor II Deficiency	↓↓ F II (Prothrombin)	Mucocutaneous bleeding	↑↑ PTT ↑↑ PT F II assay	FFP ($T_{1/2}$ =84 hrs) PCC
Congenital afibrinogenemia	↓↓ F I (Fibrinogen)	Bleeding	↑↑ PTT,↑↑ PT ↑↑ TT, reptilase F I assay	**Cryo-precipitate FFP** ($T_{1/2}$ =2-4 days)
Congenital dysfibrinogen-emia	Qualitative F I abnormality	Mild bleeding & thrombotic disorders	↑↑ PTT,↑↑ PT ↑↑ TT, reptilase Normal FI %	**Cryo-precipitate FFP** ($T_{1/2}$ =2-4 days)
Factor XIII Deficiency	↓↓ F XIII (fibrin-stabilizing factor)	Mild bruising, ***delayed separation of umbilical cord***, poor wound healing	***All routine tests are normal*** (5M urea test) ↓↓ F XIII	**Cryo-precipitate FFP** ($T_{1/2}$ =5-7 days)
Antiplasmin or PAI deficiency	↓↓ PAI ↓↓Antiplasmin	Mucocutaneous bleeding	↓↓ ELT Specific assay	FFP

Acquired Coagulation disorders:

A) **Vitamin K deficiency:** [Vit. K dependent factors = II, VII, IX, X⟶↑↑ PTT,↑↑ PT]
Hemorrhagic disease of the NB, fat Malabsorption, prolonged use of broad-spectrum antibiotics

B) **Liver disease:** [All coagulation factors (except VIII) are synthesized in the liver⟶↑↑ PT, PTT]

C) **DIC**

D) **Anticoagulants**

E) **Acquired Inhibitors of coagulation:**
- Idiopathic (?viral infection)
- Antiphospholipid Syndrome
- Coagulation factor therapy

Von Willebrand Disease (Vascular hemophilia)

Definition

It is the most common hereditary bleeding disorder (1% of population) due to deficiency (Type 1), absence (Type 3) or qualitative change in vWF (Type 2).

Etiology

Genetic disease (AD)

vWF is an acute phase reactant (↑↑ in stress)

Physiology of vWF

☒ **Structure:** large multimeric glycoprotein.

☒ **Synthesis:** a. ***Endothelial cells*** ⟶ released into plasma & subendothelial matrix
b. ***Megakaryocytes*** ⟶ stored in platelets

☒ **Function:** a. ***Platelet adhesion:*** through binding to platelet GPIb receptors ⟶ ↑↑ BT
b. ***Carrier of* VIII:C:** preventing its destruction by APC ⟶ ↑↑ PTT

Clinical picture (♀ > ♂)

- Mucocutaneous bleeding (epistaxis, bleeding gums, post-tonsillectomy & post-tooth extraction bleeding, menorrhagia) & easy bruising
- Hemartrosis is rare
- No bleeding with stressful procedures (childbirth, appendicectomy), Why?

Investigations

vWF in stress)

- Coagulation time & PTT: ↑↑ , Bleeding time: ↑↑, PT& TT: normal
- Platelet count: ↓↓ in type 2B & in platelet type (pseudo-) vWD "indistinguishable"
- Platelet function (RIPA = ristocetin induced platelet aggregation): impaired
- Factor VIII assay: may be ↓↓
- vWF antigen
- vWF activity (Ristocetin cofactor activity=vWF:RCo): patient plasma + normal platelet + ristocetin ⟶ if ↓↓ vWF ⟶ ↓↓ platelet aggregation

Treatment

- Desmopressin (DDAVP): ↑↑ release of vWF from the endothelium ⟶ ↑↑vWF & F VIII
- Cryoprecipitate (vWF& FVIII). Recombinant vWF may be available soon
- Antifibrinolytic agents (ε-aminocaproic acid): in dental bleeding & epistaxis

	Type 1	Type 3	Type2A	Type 2B	Type2M	Type2N	PT-vWD
vWF:Ag	↓↓	Absent	↓↓	↓↓	↓↓or N	↓↓or N	↓↓
vWF:RCo	↓↓	Absent	↓↓↓	↓↓	↓↓↓	↓↓or N	↓↓
F VIII	↓↓or N	↓↓↓	↓↓or N	↓↓or N	N	↓↓↓	↓↓or N
RIBA	↓↓	Absent	↓↓	N	↓↓	N	N
LD RIPA	Absent	Absent	Absent	↑↑	Absent	Absent	↑↑
Platelet	N	N	N	↓↓	N	N	↓↓
DDAVP	Good	No	Poor	↓↓ PLT	Poor	Poor	↓↓ PLT
vWF conc	Good						↓↓ PLT
Rx	DDAVP vWF conc	vWF conc	vWF conc DDAVP	vWF conc	vWF conc	vWF conc DDAVP	PLT
Multimer	N but ↓↓	Absent	Abnormal	Abnormal	N but↓↓	N but↓↓	Abnormal

☒ Type 2A is caused by abnormal proteolysis of vWF ⟶ ↓↓vWF:Ag & activity
☒ Type 2B is caused by hyperactive vWF ⟶ spontaneous binding to PLT ⟶ ↓↓vWF&plt
☒ Type 2M is caused by ↓↓ platelet-binding function of vWF
☒ Type 2N is caused by ↓↓ F VIII-binding function of vWF ***(autosomal hemophilia)***
☒ Platelet type vWD is caused by hyperactive platelet GPIb receptors (reverse of type

Anticoagulants

Indications

1. Deep venous thrombosis
2. Pulmonary embolism
3. Prosthetic valve
4. Extracorporeal circulation (HD, ECMO...)
5. DIC

Low molecular weight heparin (LMW):
Enoxaparin (Clexane)
Dose SC
Therapeutic: 1 mg/Kg/12 hrs
Prophylaxis: 0.5 mg/Kg/12 hrs
Monitoring: (**Not** PTT)
Factor X inhibition assay
LMW heparin level
Advantages: less bleeding complications

Contraindications

1. Active hemorrhage
2. Bleeding tendency (ITP, hemophilia...)
3. Recent head trauma / surgery, ICH
4. Uncontrolled hypertension
5. Bacterial endocarditis

Classifications

	Heparin	Oral anticoagulant (warfarin)
Source	Natural (GAG in mast cells)	Synthetic
Action	↑↑ AT III → # II, X, IX, XI Direct anti-thrombin	Competes with Vit.K → # II, VII, IX, X, (Ptn C& S)
Route	Parenteral (IV, SC)	Orally
Onset	Immediate	Delayed 1-2 days (As it 1st # Protein C & S)
Duration	4-6 hours	4-7 days
Dose	☒ 75-100 U/Kg/ 4-6 hrs or ☒ 20-30 U/Kg/hour	0.1-0.2 mg/Kg/day
Monitoring	PTT (1.5-2.5 times)	PT, INR (2-3)
Antidote	Protamine sulfate [1mg for 100U] FFP	Vitamin K (IV, SC or oral), **Not IM** FFP
Pregnancy	Safe	Teratogenic (cartilages)
Lactation	Safe	Safe

INR = International normalized ratio (N = 1): It allows comparison of PTs (reagents & instruments)

Thrombolytic therapy

Definition

Lysis of recently formed blood clots by enzymatic digestion through generation of plasmin (i.e., activation of endogenous plasminogen)

Uses

Pulmonary embolism, DVT, arterial occlusion & vascular access patency (central catheters & arteriovenous fistulas). The clot should be relatively fresh (< 3-5 days)

Drugs

Streptokinase, urokinase, tissue plasminogen activator (rTPA)
rTPA is more fibrin specific

Monitoring

FDPs

Side effects

Bleeding

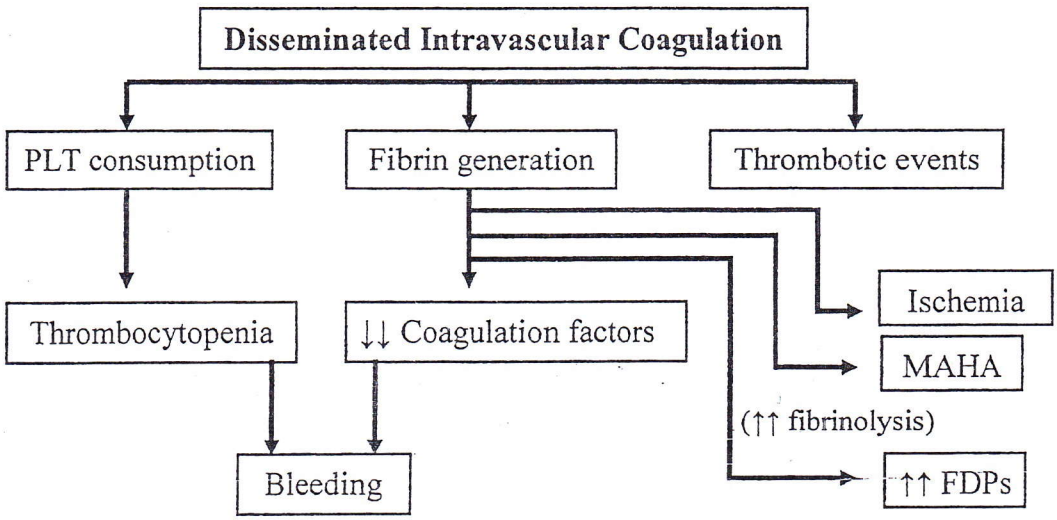
Disseminated Intravascular Coagulation

(Consumptive Coagulopathy)

Definition

DIC is characterized by widespread intravascular coagulation leading to:

- Consumption of platelet & coagulation factors ⟶ bleeding
- Intravascular fibrin deposition
  - Tissue ischemia & necrosis
  - Microangiopathic hemolytic anemia (MAHA) & thrombocytopenia
- Activation of fibrinolysis ⟶ FDPs



Etiology

1. **Septicemia:** (endotoxins, vascular injury, platelet injury, WBC activation, shock) Meningococcemia (Purpura fulminans), G-ve (Hemophilus), G+ve (GBS) sepsis
2. **Shock:** (hypotension, impaired tissue perfusion)
3. **Severe dehydration:** (vascular stasis)
4. **Snake & insect bites**
5. **Severe head injury:** (release of thromboplastin)
6. **Severe collagen-vascular disease, IBD**
7. **Burn, fracture (fat embolism), crush injury**
8. **Malignancy:** (Acute promyelocytic leukemia M3, neuroblastoma)
9. **MAHA:** (HUS, TTP, renal vein thrombosis)
10. **Hereditary thrombophilia** (AT III & protein C deficiency)
11. **Hyperthermia/ hypothermia**
12. **Incompatible blood transfusion**
13. **Acute graft rejection**
14. **Neonatal causes:** (PIH, RDS, NEC, GBS, Rh incompatability)

Clinical picture (Critically ill)

- Picture of the cause (sepsis, shock, GE…)
- Bleeding: Purpura, ecchymoses, puncture sites, internal hemorrhage
- Thrombosis: necrotic skin patches

Investigations

- Coagulation time, PT, PTT, TT, bleeding time: prolonged
- Platelet count& Factors I, II, V, VIII: ↓↓
- CBC: fragmented RBCs (burr & helmet cells)
- FDPs & D-dimer: ↑↑

Treatment

A) **Treatment of the cause** (sepsis, shock, dehydration)
B) **Replacement therapy:**
Whole blood (anemia)
FFP (coagulation factors)
Cryoprecipitate (fibrinogen)
Platelet (thrombocytopenia)
APC (in cases of sepsis & purpura fulminans)
C) **Heparin** 75-100 U/Kg/ 4-6 hrs: for thrombotic events & purpura fulminans
D) **Exchange transfusion**: for removal of toxins & addition of deficient factors

Prognosis

Depends on the primary etiology

Thrombotic Disorders

(Thrombophilia)

A) Hereditary predisposition to thrombosis

Etiology

1. Protein C deficiency

Protein C is converted to activated protein C (APC) by thrombin-thrombomodulin complex
APC ⟶ inactivates aV & aVIII (protein S acts as cofactor)

C/P:

- Neonatal period: purpura fulminans during 1st few hours (DD: neonatal sepsis)
- Later: thromboembolic disease (Less severe)

Rx:

- Neonatal period ⟶ FFP (source of protein C) or recombinant APC
- Later ⟶ long term warfarin therapy (INR= 3-5)

2. Protein S deficiency

3. Anti-thrombin III deficiency

C/P: Thromboembolic disease in adolescence
Rx: Heparin & warfarin

4. Factor V Leiden (Resistance to APC): mutation of factor V gene ⟶ resistant aV

5. Prothrombin gene mutation (G20210A): ↑↑ prothrombin synthesis

6. Homocystinuria

Diagnosis

- Clinical picture
- Family history
- Specific assay (protein C& S and Anti-thrombin III)
- Genetic analysis (factor V leiden & prothrombin gene mutation)

Other inherited thrombotic disorders:

1. Thrombomodulin deficiency
2. TPA deficiency
3. Dysfibrinogenemia
4. ↑↑ PAI-1
5. ↑↑ Levels of factors VIII, IX, X, XI

B) Acquired predisposition to thrombosis

Antiphospholipid Abs react with components used in coagulation screening tests (↑↑ PTT)

Etiology

1. Antiphospholipid syndrome

Definition: It is systemic autoimmune disease characterized by:

- Thrombosis
- Recurrent fetal loss
- ↑↑ Level of antiphospholipid antibodies (lupus anticoagulant & anticardiolipin antibody)

Classification:

a. Primary: isolated
b. Secondary* (underlying disease): SLE, infections

C/P: Thromboembolic disease
Investigations: ↑↑ PTT, specific assay
Rx: anticoagulant ± aspirin

2. Nephrotic syndrome (Urinary loss of protein C& S and Anti-thrombin III)
3. Congenital cyanotic heart disease (↑↑ Viscosity)
4. Severe dehydration& shock
5. DIC
6. Prolonged immobilization (Fracture, postoperative)
7. Sickle cell anemia (Stasis)
8. Vessel injury (Catheters, trauma, thermal injury & IV contrast)
9. Vasculitis (Kawasaki, SLE)
10. Paroxysmal nocturnal hemoglobinuria
11. TTP (Thrombotic thrombocytopenic purpura)
12. Drugs: (oral contraceptives, estrogen, prednisone)

Presentation

1. Deep venous thrombosis (Pain, swelling & tender calf muscles)
Rx: Rest, elevation, heparin followed by warfarin

2. Arterial thrombosis
Rx: Thrombolytic therapy or surgical thrombectomy

3. Stroke (Rapidly developing signs of focal disturbance of cerebral function with symptoms lasting > 24 hrs with no apparent cause other than of vascular origin)

4. Pulmonary embolism
Rx: Heparin or thrombolytic therapy, intracaval filter, pulmonary embolectomy

Purpura

Definition

It is small hemorrhage into the superficial layers of the skin producing areas of purple discoloration which do not blanch on pressure. Minute spots of 1-2 mm are called petichiae and larger areas of 1-2 cm are called ecchymoses

Classification

A) Non-thrombocytopenic purpura (Vascular or platelet dysfunction)
B) Thrombocytopenic purpura (Platelet count < 150.000/ mm^3)

A) Non-thrombocytopenic Purpura

1. Vascular

Congenital	Acquired
1. Ehler-Danlos syndrome ▪ Hyperelasticity of the skin ▪ Hyperlaxity of joints **2.** Marfan syndrome **3.** Osteogenesis imperfecta **4.** Ataxia telangiectasia	**1.** Immune ▪ Henoch-Schonlein vasculitis ▪ SLE, PAN **2.** Infection ▪ Meningococcemia ▪ Infective endocarditis **3.** Steroids (Cushing' syndrome) ▪ Exogenous ▪ Endogenous **4.** Scurvy

2. Platelet dysfunction (Thrombocytopathy)

Congenital	Acquired
A) Defects of adhesion ▪ vWD ▪ Bernard-Soulier (AR) *Defect*:↓↓ platelet GPIb receptors (vWF) *Features*: **Giant platelet** Thrombocytopenia ↓↓ RIPA **B) Defects of aggregation (Glanzmann disease)** *Defect*: ↓↓ Platelet fibrinogen receptors *Features*: Normal platelet count Normal adhesion (normal vWF) Defective aggregation **C) Defects of platelet secretion** ▪ Dense body deficiency (↓↓ ADP) ▪ Gray platelet $ (↓↓ Plt α granules) **D) ↓↓ PF3**	**1.** Drug induced (Not dose-related) (# cyclo-oxygenase enzyme) ▪ Aspirin ▪ NSAIDs (indomethacin, ibubrufen…) ▪ Valproate **2.** Uremia (uremic toxins) Bleeding is an indication of dialysis Dialysis can correct this defect **3.** Systemic diseases ▪ Chronic ITP ▪ SLE ▪ Leukemia ▪ Congenital cyanotic HD ▪ Liver cell failure Arachidonic acid ↓ *cyclo-oxygenase* Thromboxane A_2 (↑↑ aggregation)
Rx: **a.** Desmopressin (DDAVP) "vWF" **b.** Platelet transfusion **c.** Stem cell transplantation	

B) Thrombocytopenic Purpura

1. Decreased production (↓↓ Megakaryocytes)

Congenital	Acquired
1. Fanconi anemia 2. Thrombocytopenia with absent radii (TAR syndrome) ▪ Isolated megakaryocytic defect ▪ Early onset (neonatal period) ▪ No chromosomal abnormalities 3. Thrombopoietin deficiency **Rx:** FFP 4. Amegakaryocytic thrombocytopenia 5. Wiskott-Aldrich syndrome (XLR) ▪ Immunodeficiency ▪ Eczema ▪ Thrombocytopenia **(Tiny platelets)**	1. Aplastic anemia 2. Bone marrow infitration ▪ Malignancy ▪ Myelofibrosis ▪ Osteopetrosis 3. Megaloblastic anemia ▪ Folic acid deficiency ▪ Vitamin B_{12} deficiency 4. Sepsis

2. Increased destruction (Normal / ↑↑ Megakaryocytes)

Congenital	Acquired
1. Kasabach-Merritt $ ▪ Large cavernous hemangioma ▪ Platelet trapping& destruction ▪ MAHA Rx: Laser photocoagulation, steroids, radiation or INF-α_2 (anti-angiogenic) 2. Bernard-Soulier $ (Giant platelets) 3. Wiskott-Aldrich $	**A) Immune** ▪ ITP ▪ SLE ▪ Evans $ (autoimmune anemia & thrombocytopenia) ▪ Drug mediated (α-methyl dopa) *Mechanism:* Drug acts as a ***hapten*** **B) Non-immune** ▪ Hypersplenism (sequestration) ▪ Infection (sepsis) ▪ Microangiopathic diseases (HUS, TTP, renal vein thrombosis, DIC)

Immune neonatal thrombocytopenia: (Good prognosis 2-4 months. Why?)

Causes

1. **Maternal autoantibodies** (Transplacental passage of maternal Ab)
   - a. **SLE**
   - b. **ITP**
   - c. **Drug induced**

   ↓↓ Maternal platelet count
   Milder C/P than NATP
   Rx: maternal steroid, IVIG

2. **Neonatal alloimmune thrombocytopenia (NATP)**"Rh incompatibility analog"

Cause: Maternal allantibodies against fetal platelet antigen acquired from the father
The 1st baby is usually affected

C/P: Petichiae, mucocutaneous hemorrhage, ICH

Diagnosis Normal maternal platelet count
Maternal Ab against father's platelets

Monitoring of fetal platelet count (percutaneous umbilical blood sampling = PUBS)
± platelet transfusion

Rx *Antenatal* IVIG to the mother (2nd trimester) ⟶ Elective CS
Neonate Blood transfusion, washed platelet transfusion (from the mother)
IVIG, steroid

Idiopathic Thrombocytopenic Purpura (ITP)

Definition

It is the most common cause of acquired thrombocytopenic purpura in children. It is caused by immune destruction of platelets

Etiology (= evidence of immune nature)

- Preceded by viral infection (URT infection)
- Interval between infection & presentation (1-4 weeks)
- Platelet autoantibodies (in some cases)

Rx does not affect the natural history of the disease

Pathogenesis

Antibody-coated platelets are destructed in the splenic sinusoids (recognized by Fc receptors)

Clinical picture (Age = 1-4 years, Onset = sudden)

Splenomegaly is rare

- Pupura (petichiae & ecchymoses)
- Mucocutaneous bleeding (epistaxis, bleeding gums, GIT, hematuria) & ICH
- Easy bruising
- No organomegaly, No lymphadenopathy, No pallor (except with severe bleeding)
- 20% develop chronic ITP (persistent > 6 months)

Investigations

- CBC: ↓↓ platelet, normal Hb & WBCs (Theoretical safe level = 20.000/ mm^3)
- Bone marrow aspirate (Not routine in straight forward cases)
- Normal or ↑↑ megakaryocytes with defective budding (Not pathognomonic of ITP)
- Anti-platelet antibodies: may be detected in some patients
- Coombs' test (Evans syndrome)
- ANA, ESR: ITP may be the **1st manifestation** of collagen vascular diseases (SLE)

Treatment

*There is **No general agreement** about management of ITP*
Platelet transfusion is contraindicated unless life-threatening bleeding occurs
ICH remains a rare complication
There is no relationship between platelet count & severity of ITP

A) Mild cases (cutaneous): Avoid trauma & salicylates with close observation & F/U

B) Treatment options:

1. **IVIG:** 400 mg/Kg/day for 5 days Or 0.8-1 g/Kg/day for 1-2 days
   Advantages: Rapid ↑↑ platelet count
   Disadvantages: Expensive, ↑↑ aseptic meningitis
2. **Prednisone:** 2 mg/Kg/day for 2-3 weeks or until platelet >20.000/ mm^3 with rapid tapering (guided by clinical & lab response)
3. **IV anti-D antibodies:**
   Requirements: Rh +ve patient with Hb > 10g %
   Mechanism: mild hemolytic anemia ⟶ Saturation of splenic Fc receptors with RBC-Ab complexes ⟶ ↓↓ platelet destruction
4. **Splenectomy** (Site of Ab production& platelet destruction)
   Indications:
   - Severe chronic ITP in older child > 4 years
   - Acute ITP with life-threatening bleeding not corrected by steroids, IVIG or platelet transfusion
5. **Platelet transfusion** (When?)

C) **Chronic ITP** (persistent thrombocytopenia > 6 months)

- Exclude other causes e.g., SLE, vWD 2B, Wiskott-Aldrich $
- Steroids, other immunosuppressives (e.g., azathioprine, cyclosporine, vincristine)
- IVIG
- Anti-D therapy
- Splenectomy

Thrombocytosis

Definition

Platelet count > 750.000/ mm^3

Etiology

A) **Primary (= Myeloproliferative syndrome)**
Overproduction of platelets in cases of polycythemia vera, chronic myeloid leukemia (CML) & essential thrombocythemia

B) **Secondary (Reactive):**

1. Iron deficiency (EPO has some structural homology with throbopoietin)
2. Acute hemorrhage
3. Chronic hemolytic anemia
4. Postsplectomy (& asplenia) [1/3 platelets are sequestrated in the spleen]
5. Collagen-vascular diseases (Kawasaki, systemic-onset JRA, PAN, IBD)
6. Response to exercise, trauma & surgery
7. Response to drugs (adrenaline)
8. Recovery from thrombocytopenia
9. Recovery from suppressive drugs
10. Nephrotic syndrome

Clinical picture

- ***Asymptomatic*** in the majority of patients
- ***Thrombotic*** manifestations (e.g., venous thrombosis, pulmonary embolism…)

Investigations

- CBC: ↑↑ platelet count
- Platelet function: normal

Treatment

- Asymptomatic: No Rx
- Thrombotic manifestations: Anti-platelet therapy
  - ☒ Acetyl salicylic acid (Aspirin) # cyclo-oxygenase enzyme: 80-160 mg/day
  - ☒ Dipyridamol
- Plateletpheresis (thrombocytapheresis)

Anemia

Definition

It is reduction in hemoglobin concentration or hematocrit below normal for age & sex.
More accurately, it is defined as reduction in red cell mass ⟶ ↓↓ O_2 delivery to tissues

Pathophysiology

1. ↑↑ Cardiac output (↑↑ HR, ↑↑ VR, ↑↑ SV) ⟶ Hyperdynamic circulation
2. ↑↑ Pulmonary function (tachypnea)
3. ↑↑ O_2 delivery to tissues "shift to right" due to ↑↑ 2,3 DPG (2,3 diphosphoglycerate)
4. ↑↑ Erythropoietin (renal hypoxia) ⟶ BM hyperactivity (6-8 folds)
5. ↑↑ Plasma volume
6. Redistribution of blood to the vital organs (brain & heart)

Clinical picture *(depends on **severity** & **rate** of development)*

A) Symptoms

- Fatigue
- CVS: exertional dyspnea, palpitation, HF
- CNS: headache, tinnitus, syncope, lack of concentration
- Renal: polyuria (mild proteinuria)

B) Signs

- Pallor
- Hyperdynamic circulation: tachycardia, big pulse volume, ↑↑ heart sounds, hemic murmurs & HF

C) Picture of the cause

- Iron deficiency anemia: koilonychia (spoon-shaped nails)
- Megaloblastic anemia (B_{12}): neurological manifestations
- Hemolytic anemia: jaundice, organomegaly
- Aplastic anemia: bleeding & fever
- Malignancy (leukemia): bleeding, fever, HSM & lymphadenopathy

Classification

A) Morphological (according to MCV)

Microcytic (MCV < 75 fL)	**Normocytic** (MCV=75-90 fL)	**Macrocytic** (MCV > 100 fL)
Iron deficiency anemia	Hemorrhage(internal/external)	Normal newborn
β-Thalassemia trait	Hemolysis(membrane/enzyme)	Folic acid & B_{12} deficiency
β-Thalassemia major	Bone marrow infiltration	↑↑ Erythropoiesis (↑↑ Retics)
α-Thalassemia trait	Renal failure	Diamond-Blackfan & Pearson
HbH disease (β_4)	Collagen-vascular diseases	CDA
Chronic disease (infection)	Chronic disease (infection)	Aplastic anemia (cons. /acq.)
Lead poisoning	Hypersplenism	Myelodysplastic syndromes
Sideroblastic anemia	Sequestration	Orotic aciduria
Atransferrinemia		Lesch-Nyhan syndrome
Copper deficiency		Thiamine-responsive megalo-
Malabsorption (Celiac)		Liver disease-Hypothyroidism
Iron malabsorption		Vitamin B_6 deficiency

B) Etiological

Anemia

↓↓Production

↓↓Precursors

- **Pure red cell aplasia** → Congenital / Acquired
- **TEC**
- **Pancytopenia**
  - **Aplastic**
    - **Constitutional**
      - Fanconi anemia
      - Dyskeratosis congenital
      - Shwachmann-Diamond $
      - Amegakaryocytic thrombocytopenia
    - **Acquired**
      - Idiopathic
      - Viruses (Hepatitis, CBV, EBV, HIV)
      - Drugs (predictable/idiosyncrasy) Radiation
      - Paroxysmal nocturnal hemoglobinuria
  - **BM infiltration**
    - Malignancy (leukemia)
    - Osteopetrosis
    - Myelofibrosis
  - **Megaloblastic**
    - Folic acid
    - Vitamin B_{12}

Normal precursors

- Chronic disease → Infection / Inflammation
- CRF
- Dyserythropoiesis → 1ry (CDA) / 2ry

Specific factors

- Fe, B_{12}, B_1, B_6, B_2
- Vit. C, Cu, proteins
- Folic acid

- Megaloblastic anemia
- Thalassemia
- Sideroblastic anemia
- PNH
- Malignancy

Blood loss (external/ internal)

↑↑ Destruction

Intracorpuscular

- **Membrane**
  - **Congenital**
    - H. Spherocytosis
    - H. Elliptocytosis
    - H. Pyropoikilocytosis
    - H. Stomatocytosis
  - **Acquired**
    - PNH
- **Enzyme**
  - **Glycolysis**
    - Pyruvate kinase
    - PFK
    - Hexokinase
  - **HMP shunt**
    - G6PD
    - Glutathione peroxidase
    - Glutathione deficiency
- **Hemoglobin**
  - **Quantitative**
    - Thalassemia
  - **Qualitative (hemoglobinopathy)**
    - Sickle cell
    - HbC
    - Unstable Hb

Extracorpuscular

- **Immune**
  - Passive (Allo-Ab)
    - HDN → Rh / ABO / Minor
    - Mismatched blood
      - 1ry (Idiopathic)
      - 2ry
        - Infection
        - malignancy
        - Collagen-vascular
        - Drugs
  - Active (Auto-Ab)
- **Non-immune**
  - MAHA
    - HUS
    - TTP
    - DIC
    - Renal VT
  - Infections
    - Malaria
    - G-ve sepsis
    - Clostridium
  - Hypersplenism
  - Wilson's
  - Chemicals
    - Heavy metals
    - Oxidants

Pure Red Cell Anemia

Definition

It is deficiency or absence of **red cell precursors** in an otherwise normal bone marrow

Classification

A) Congenital pure red cell anemia (Diamond-Blackfan $)
B) Acquired pure red cell anemia

Congenital Pure Red Cell Anemia

(Congenital hypoplastic anemia-Diamond-Blackfan $)

Etiology

- Sporadic: the majority
- Inherited: 15% (AD, AR)

Clinical picture (Onset = usually in 1st 3 months)

- ***Pallor***
- ***Hydrops fetalis*** (Fetal anemia)
- ***Physical anomalies:*** short stature, triphalangeal thumb, UL & cardiac anomalies
- ***Transfusion dependent*** ⟶ hemosiderosis ⟶ HSM "Iron overload"
- ***Spontaneous remission*** occurs in 20 % of patients
- ***Premalignant condition*** (AML)

Investigations

- CBC: anemia (↓↓ Hb %), **macrocytic** (MCV ↑↑)
  Platelet & WBC: initially normal (↓↓ with hypersplenism)
- ↓↓ Reticulocytic count
- ↑↑ Serum iron
- ↑↑ Erythropoietin
- ↑↑ Hb F (hematologic stress)
- Normal RBC survival
- ↑↑ RBC adenosine deaminase activity (ADA)
- Normal chromosomal studies (DD: Fanconi anemia)
- BM examination (aspirate/ biopsy): ↓↓ red cell precursors (↑↑ Apoptosis)
  Normal myeloid & megakaryocytic series
  ↑↑ M/E ratio > 10

Normal M/E ratio 2:1- 4:1

Treatment

- Chronic transfusion therapy + iron chelating therapy (Deferoxamine or Deferiprone)
- Prednisone (2 mg/Kg/day): monitored with Hb % & Retics (response rate = 75 %)
- Other immunosuppressive agents (cyclophosphamide, cyclosporin)
- Hematopoietic stem cell transplantation (HLA-matched donor)

Complications

- Hemosiderosis
- Malignancy
- Steroid & immunosupprssive toxicity
- Complication of HSCT

Pearson marrow-pancreas $ ***Etiology:*** mt DNA deletion
Features: ***Pathology:*** Pancreatic fibrosis & BM changes

1. Congenital hypoplastic anemia
BM⟶ Vacuolization of erythroid & myeloid precursors
Ringed sideroblasts (It is a form of congenital sideroblastic anemia)
2. Pancreas: IDDM, exocrine pancreatic dysfunction (FTT, Malabsorption & chronic diarrhea)
3. Others: Muscle & neurological impairment
CBC: anemia (macrocytic), neutropenia & thrombocytopenia ***Rx:*** Blood transfusion

Acquired Pure Red Cell Anemia

A) Transient Erythroblastopenia of Childhood (TEC) (most common)

It is acquired red cell aplasia due to transient **immunologic suppression of erythropoiesis** usually following viral infection (Not Parvovirus B 19)

	Diamond-Blackfan S	TEC
Frequency	Rare	More common
Age at diagnosis	90 % by 1st year	6 months-3 yrs
Etiology	Genetic	Acquired (viral/ idiopathic)
Congenital anomalies	Present (triphalangeal thumb, UL, cardiac, renal)	Absent
HB %	3-4 %	3-9 %
Transfusion dependence	Transfusion or steroid dependent	Not
MCV	Macrocytic > 100 fL	Normocytic
Hb F	↑↑	Normal
RBC ADA activity	↑↑	Normal
Treatment	Steroids, Packed RBC, HSCT	Packed RBC if required
Prognosis	Spontaneous recovery (only 20 %)	Spontaneous recovery (wks-months)

B) Red cell aplasia associated with chronic hemolysis

Parvovirus B 19 is cytotoxic to RBC precursors ⟶ transient ↓↓ erythropoiesis < 2 wks
It is self-limited condition; unnoticed in normal individuals (RBC life span=110-120d)
It causes aplastic crisis in patients with chronic hemolytic (short RBC life span)

C) Red cell aplasia associated with immunodeficiency (Congenial/acquired)

Due to persistent Parvovirus B 19 infection
Diagnosis: Serology (IgM), viral DNA (PCR), Prenatal (viral DNA in fetal blood)
Rx: IVIG

D) Red cell aplasia associated with hydrops (Non-immune hydrops)

It is due transplacental infection with Parvovirus B 19

E) Red cell aplasia associated with other diseases (Ab mediated)

SLE, CLL, lymphoma

F) Red cell anemia associated with some drugs (e.g., chloramphenicol)

- ***NB: Hematological toxicity of chloramphenicol:*** (2 effects)

	Pancytopenia	Erythroid depression
Dose	Idiosyncrasy (not dose-related)	Dose-related
Genetics	Genetic predisposition	No
Route	Follows **oral** administration	Any
Mechanism	Formation of toxic metabolite by intestinal bacteria	Inhibition of iron uptake by normoblasts Inhibition of iron incorporation into Hb

Dyserythropoiesis

(Ineffective erythropoiesis)

Definition

It is erythroid hyperplasia with production of defective erythrocytes which are destroyed within the **bone marrow** or immediately after release into the **peripheral** blood. There is marked discrepancy between the BM picture "hyperplasia" & periphery "anemia"

Classification

A) Congenital dyserythropoietic anemia

B) Secondary dyserythropoietic anemia (Thalassemia, megaloblastic, sideroblastic, PNH, malignancy)

Congenital Dyserythropoietic Anemia

Definition

It is a rare disorder characterized by ineffective erythropoiesis, macrocytic anemia & unique BM "RBC precursor" abnormalities (multinuclearity & abnormal chromatin patterns)

Etiology (Genetic AR /AD)

Impaired membrane protein glycosylation

Clinical picture (Onset = may present in the neonatal period)

- Variable degrees of anemia
- Intermittent jaundice
- Splenomegaly

Immunodeficiency
Congenial/acquired

Investigations

- CBC: anemia (↓↓ Hb %), macrocytic (MCV ↑↑). Platelet & WBC: normal
- ↓↓ Reticulocytic count
- ↑↑ Serum iron (Ineffective erythropoiesis)
- ↓↓ RBC survival
- ↑↑ Serum bilirubin (indirect)

DD: Hemolytic anemia but ↓↓ Retics

- BM examination (aspirate/ biopsy): Erythroid hyperplasia (↑↑ red cell precursors)
  Normal myeloid & megakaryocytic series
  ↓↓ M/E ratio

	CDA Type I	CDA Type II*	CDA Type III
Inheritance	AR	AR	AD
Chromosome	15	20	15
BM erythroblast	Binuclear Megaloblastic	Multinuclear (2-7) Normoblastic	Multinuclear (up to 12) Megaloblastic
Serology	-Ve	+Ve	-Ve
Ham test	-Ve	+Ve	-Ve
RBC i antigen agglutination	Normal	Strong	Normal
Treatment	Blood transfusion + iron chelation ± splenectomy		
	INF-α	-	-

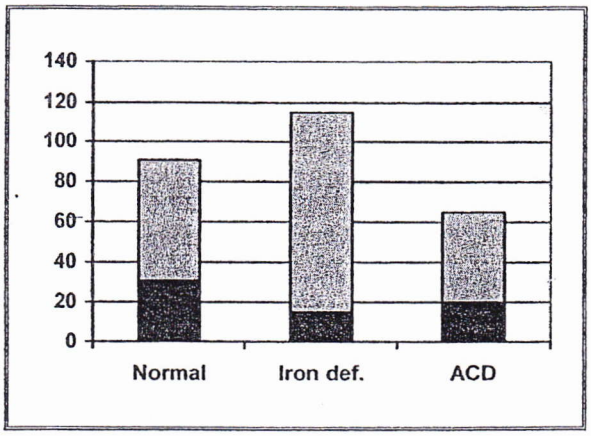
Acidified serum test (Ham test): patient's RBCs are lysed by acidified serum from normal individuals but not by the patient's own acidified serum (DD: PNH)

CDA type II is called **HEMPAS** (= **H**ereditary **E**rythroblastic **M**ultinuclearity with **P**ositive **A**cidified **S**erum test)

Anemia of Chronic Disease

Etiology

- Chronic **infection**: Bronchiectasis, TB, osteomyelitis
- Chronic **inflammation**: SLE, JRA, IBD
- **Malignancy**



Pathogenesis

- Hypoactive BM
- ↓↓ Erythropoietin *(relative to degree of anemia)*
- ↓↓ Iron utilization
- ↓↓ RBC life span (hemolysis by RES)
- Release of cytokine : INF-β, INF-γ, TNF

Clinical picture

- Anemia
- Picture of the cause

Investigations

- CBC: Normocytic normochromic anemia (may micro- hypo-), leukocytosis
- ↓↓ Reticulocytic count
- ↓↓ Serum iron, ↓↓ TIBC (Total iron binding capacity), ↓↓ iron saturation, ↑↑ Serum ferritin
- ↓↓ RBC survival
- ↑↑ Free erythrocyte protoporphyrin (FEP): ↓↓ iron utilization ⟶ ↓↓ Heme synthesis
- BM examination (aspirate/ biopsy): ↑↑ hemosiderin

Treatment

- Treatment of the cause
- Recombinant human erythropoietin [r-HuEPO]

Anemia of CRF

Pathogenesis

1. ↓↓ Erythropoietin (most important)
2. ↓↓ iron utilization
3. ↓↓ RBC life span (# of Na-K ATPase ⟶ Hemolysis)
4. ↓↓ intake: anorexia & vomiting
5. Dilutional anemia
6. Bleeding tendency (Thromocytopathy)
7. Bleeding: sampling, insertion of VA (Central catheters)
8. VA-related complications
9. Residual blood in HD machine circuits
10. Loss of folic acid in HD treatment (dialyzable)

Benefits	Complication
Avoid blood transfusions	Iron deficiency
↓↓ sensitization to HLA antigens	Hypertension
↓↓ exposure to infectious disease	Seizures
↑↑ appetite	Pure red cell aplasia
↑↑ exercise tolerance, activity	Clotting of vascular access

Clinical picture& Investigations

Treatment

- Recombinant human erythropoietin [r-HuEPO]: 50-100 units/kg SC 1-3 times/ wk
  It is indicated when Hb < 10g%
- Packed RBC (↓↓ success of renal transplantation due to sensitization)
- Dialysis or renal transplantation

Megaloblastic Anemia

Definition

Anemia due to impairment of DNA synthesis leading to delayed cell division & cellular gigantism. It is characterized by BM megaloblasts & blood macrocytes

Etiology

> 90 % are due to folic or vitamin B_{12} deficiency

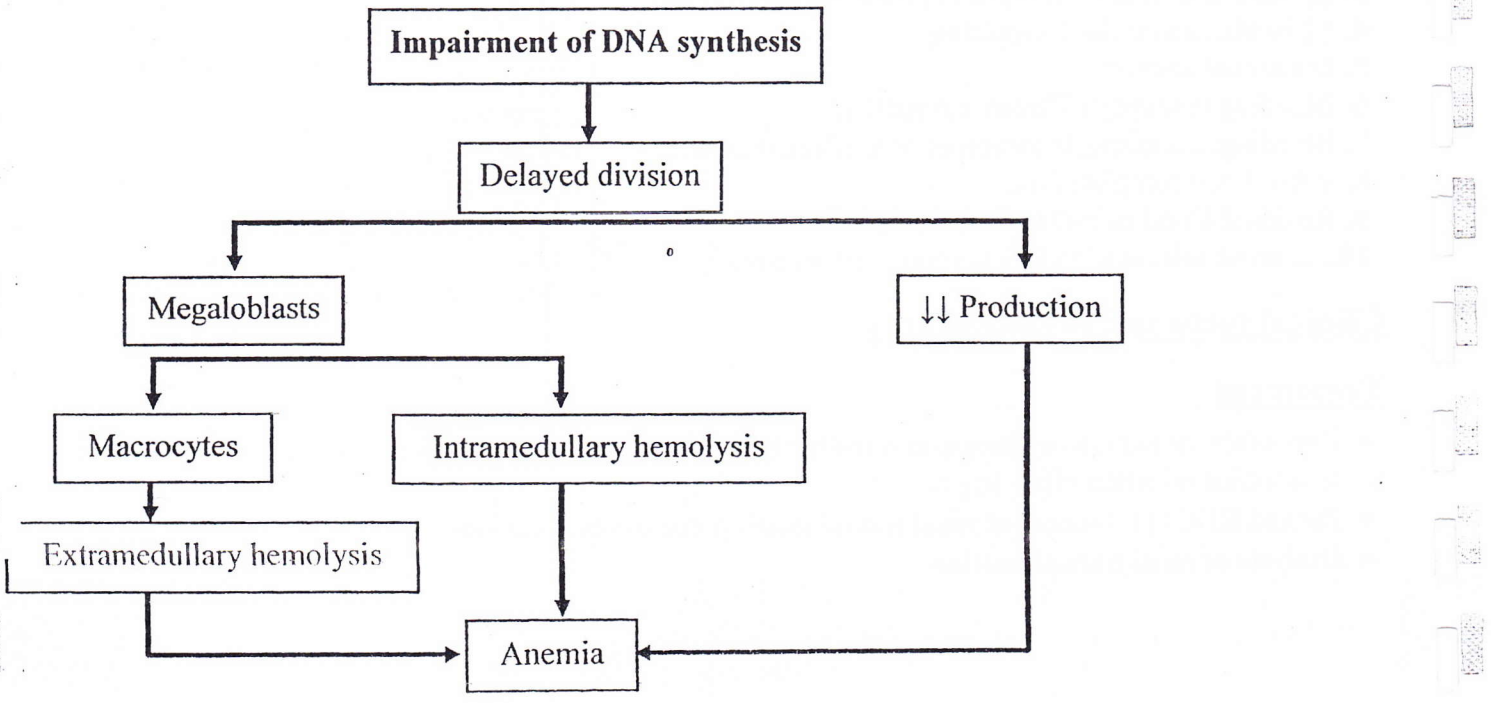
Physiology

	Vitamin B_{12}	Folic acid
Source	Animal origin (milk, meat)	Plant (green leaves) & animal (liver)
Requirements	2.5 µg / day (Stores are sufficient for 3-5 yrs)	25-35 µg / day (↑↑ in preterm, pregnancy, CHA)
Absorption	**1.** Gastric parietal cell → Intrinsic factor → IF-B_{12} complex **2.** Binding to specific receptors **3.** Absorption in **terminal ileum** (by endocytosis)	Proximal jejunum
Transport	Transcobalamin I, II, III	Plasma proteins
Functions	Two coenzyme forms: ***1. Adenosylcobalamin*** M.M.CoA → Succinyl CoA ***2. Methylcobalamin*** Homocysteine → Methionine ***3. Regeneration of THF***	Folic →* DHF →* THF (active form) [* = Dihydrofolate reductase] **1.** Biosynthesis of DNA **2.** Formation of methionine Homocystein —(B12)→ Methionine Methyl THF — THF

M.M.CoA = Methylmalonyl CoA **THF** = Tetrahydofolic acid

Pathophysiology (Nuclear-cytoplasmic dissociation)

- Impairment of DNA synthesis leading to delayed cell division & nuclear maturation
- RNA & protein synthesis in the cytoplasm are **not** affected
- Megaloblastic changes occur in all cell precursors
- Ineffective erythropoiesis, leukopoiesis & thrompopoiesis (due to lack of DNA repair)



Etiology

Deficiency of Vitamin B_{12}	Deficiency of Folic acid
↓↓ Intake Vegetarians-malnutrition	**↓↓ Intake** Goat milk-↓↓ vegetable intake- malnutrition
↓↓ Absorption **a. ↓↓ Intrinsic factor** (IF) • **Congenital pernicious anemia** (AR) Absence of IF or biologically inactive IF Normal HCl secretion by parietal cells • **Juvenile pernicious anemia** Ab against IF& parietal cells Associated with: HAM $, thyroid disease... • **Gasterectomy** • **Caustics** **b. Failure of intestinal absorption** • **Specific Vit. B_{12} malabsorption** Defective receptors for IF-B_{12} complex • **Generalized malabsorption** • **Terminal lieum disease** NEC, Crohn disease, TB enteritis, resection • **Bacterial overgrowth** • **Diphyllobothrium latum**	**↓↓ Absorption** **a. Generalized malabsorption** Celiac, short bowel... **b. Specific folic acid malabsorption** Associated with defective transport of folic acid to CNS [Megaloblastic anemia& MR]
	↑↑ Requirements ▪ Premature infants (50-200 µg/day) ▪ Pregnancy & lactation (400 µg/day) ▪ Chronic hemolytic anemia ▪ HD ▪ Malignancy ▪ Extensive skin disease (psoriasis)
↓↓ Transport Congenital absence of transcobalamin II	**Disorders of folic acid metabolism** ▪ Congenital Dihydrofolate reductase ↓↓ ▪ Dihydrofolate reductase inhibition [Trimethoprim, Methotrexate, Pyrimethamine] ▪ Anticonvulsants (phenytoin, phenobarb)
Disorders of Vit. B_{12} metabolism Deficiency of methyl- & adenosylcobalamin	

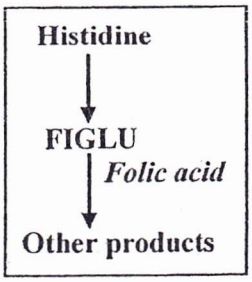
Clinical picture

A) **Hematological:** anemia, pancytopenia (infection & bleeding)
B) **GIT:** glossitis & diarrhea
C) **Neurological:** peripheral neuritis, neuropsychiatric changes & subacute combined degeneration of the spinal cord
   - Posterior column: deep sensory loss, sensory ataxia
   - Pyramidal tract: +ve Babinski sign, clonus

Neurological manifestations only in vitamin B_{12} deficiency

Investigations

- CBC: RBC → Macrocytic normochromic anemia, ↓↓ Retics
  WBC → Leukopenia, hypersegmented PNLs (shift to Rt)
  PLT → Thrombocytopenia, giant platelets
- ↑↑ Serum iron (Ineffective erythropoiesis)
- ↓↓ RBC survival
- ↑↑ Serum bilirubin (indirect)
- ↑↑ LDH
- BM examination (aspirate/ biopsy): hypercellular megaloblastic BM
- Measurement of serum folic acid & vitamin B_{12}
- Urinary excretion of methylmalonic acid (↑↑ with vitamin B_{12} deficiency)
- FIGLU test (formiminoglutamic acid): ↑↑ urinary excretion of Figlu after oral histidine indicates folic acid deficiency *(folic acid is important for Figlu metabolism)*
- Schilling test:



- ☒ IM vitamin B_{12} (1 mg) to **saturate** body stores & transcobalamins
- ☒ **Oral radioactive** vitamin B_{12} (1 µg)
- ☒ **Urine** is collected to measure excreted vitamin B_{12}
- ☒ Normally, **10-30 %** of the absorbed oral dose is excreted in urine
- ☒ ↓↓ excretion indicates ↓↓ absorption
- ☒ Give **oral IF** with radioactive vitamin B_{12}, if ↑↑ excretion ⟶ IF deficiency
- ☒ Failure of ↑↑ excretion (after IF) indicates intestinal cause of malabsorption

Treatment

*Vitamin B_{12} deficiency should be **excluded** before administration of folic acid since it may **aggravate** neurological manifestations*

- Vitamin B_{12} deficiency: IM (1000 µg) monthly [Depovit B_{12}]
- Folic acid deficiency: 0.5-1 mg/day start with low dose *[Folic acid tablet]*

Other Causes of Megaloblastic Anemia

A) Orotic Aciduria (AR)

Cause: Deficiency of orotic phosphoribosyltransferase (OPRTase)
C/P: Megaloblastic anemia, developmental delay (motor & mental)
Diagnosis: ↑↑ excretion of orotic acid (& crystalluria)
Rx: Uridine

B) Lesch-Nyhan syndrome (XL-R)

Cause: Deficiency of hypoxanthine guanine phosphoribosyltransferase (HGPRTase)
C/P: Megaloblastic anemia, developmental delay (motor & mental), self-mutilation
Diagnosis: ↑↑ serum uric acid

C) Thiamine-responsive megaloblastic anemia (AR)

Cause: Deficiency of thiamine
C/P: Megaloblastic anemia, cardiomyopathy, deafness, optic nerve atrophy
Rx: Thiamine

Iron metabolism *(Iron hemostasis is regulated mainly by absorption rather than excretion)*
Sources: organ meat, egg yolk, muscle meat, whole cereals
Requirements: 1-1.5 mg/day (diet should contain 10-15 mg/day, as normally 10-15 % is absorbed)
Absorption: in the duodenum & upper jejunum, in the ferrous state (Fe^{++}) "ascorbic acid"
Cu is important for iron absorption & mobilization
Factors affecting iron absorption:

- Needs of the body: enterocytes contain ferritin & transferrin [mucosal-block]
  ↓↓ Iron stores ⟶ ↓↓ apoferritin, ↑↑ apotransferrin ⟶ ↑↑ iron absorption
  ↑↑ Iron stores ⟶ ↑↑ apoferritin, ↓↓ apotransferrin ⟶ ↓↓ iron absorption "Fe trap & slough"
- Rate of erythropoiesis: hemolysis & hge are associated with ↑↑ iron absorption
- Dietary phytic acid, PO_4, oxalate, FA, tannic acid ⟶ ↓↓ iron absorption
- Ascorbic acid ⟶ ↑↑ iron absorption

Excretion: mainly in stools, urine, breast feeding & menstruation (0.5-1 mg/day)

Iron Deficiency Anemia

Definition

It is the **most common** cause of anemia

Iron distribution

A) **Functional:** Hemoglobin, myoglobin, enzymes (catalase, cytochrome oxidase P_{450}, monoamine oxidase = MAO)

B) **Nonfunctional:**
- Ferritin (main storage form - **reliable** index of iron storage)
- Hemosiderin (iron storage form - not present in plasma)
- Transferrin: (transport form in the plasma)

Normally, transferrin can carry 250-400 µg of iron/ dL *(= TIBC)*
Normal serum iron = 40-140 µg/dL
Normally, 30 % of TIBC is saturated

Hemosiderosis: accumulation of hemosiderin in the cells of RES with mild tissue damage
Hemochromatosis: hemosiderosis with injury of **parenchymal** cells (liver, pansreas, heart...)

Etiology

1. ↓↓ **Intake**
   Cow's milk, exclusive breast milk or powder milk without supplementation
2. ↓↓ **Absorption** (e.g., celiac disease…)
3. ↑↑ **Loss of iron (chronic blood loss)**
   - Parasitic: Ankylostoma (hookworm)
   - Sampling
   - Meckel's diverticulum
   - IBD
   - Cow's milk protein intolerance
   - Peptic ulcer & varices
   - Polyps & hemangiomas
   - Pulmonary hemosiderosis

Clinical picture (Onset ≈ 6 months)

Preterm require iron supplementation once they are on full enteral feeds

A) **Hematological:** anemia

B) **Neurological:**
- ↓↓ alertness, attention span & intellectual functions
- Stroke (RBC wall rigidity)
- Pica (ingestion of non-nutrient materials)
- ?? ↑↑ frequency of breath-holding attacks

C) **Epithelial changes**
- Nails: thin, lusterless, brittle, longitudinal ridges, koilonychia (spoon-shaped)
- Glossitis & angular stomatitis
- Hair: dry & brittle

D) **Splenomegaly** (10 %)

Investigations

- CBC: RBC → Microcytic hypochromic anemia (↓↓ MCV & MCH), ↑↑ **RDW**, Anisocytosis, poikilocytosis, Retics (normal or ↓↓ but ↑↑ after Rx)
  WBC → Normal (eosinophilia may be present. Why?)
  PLT → Thrombocytosis
- ↓↓ Serum iron with ↑↑ TIBC, ↓↓ iron saturation, ↑↑ TfR
- ↓↓ Serum ferritin < 10 ng/ml (more accurate) ⇒ **The gold standard in documenting total iron stores is BM aspirate**
- ↑↑ Free erythrocyte protoporphyrin (FEP)
- BM examination (aspirate/ biopsy): Hypercellular (erythroid hyperplasia)
- Investigation of the cause (e.g., Stool analysis, BAL, normal Hb electrophoresis...)

Treatment

Iron therapy should be continued for at least 3 months

1. **Treatment of the cause**
2. **Dietary** supplementation
3. **Iron therapy** *(6 mg elemental iron / Kg / day)*
   - **a. Oral** (ferrous gluconate or ferrous sulfate)
     Give in 3 divided doses in between meals (Vitamin C helps iron absorption)
   - **b. Parenteral** (Iron dextran)
     Indicated in cases of malabsorption, intolerance to oral iron & non-compliance
     Not more rapid. Not more effective

Response to iron therapy

Time after Iron Rx	Response
12-24 hrs	Replacement of intracellular enzymes
36-48 hrs	BM response (hyperplasia)
48-72 hrs	Reticulocytosis
4-30 days	↑↑ Hemoglobin
1-3 months	Repletion of stores

4. **Blood transfusion** *(Indicated **only** in very severe cases)*
   - Rapid hematological response can be achieved by iron therapy
   - Risky procedure: volume overload, HF
   - In severe cases [Packed RBC 2-3 ml/Kg + furosemide] "can be repeated"

Microcytic Hypochromic Anemias

Etiology

1. **Iron deficiency anemia**
2. **β-Thalassemia trait:** ↑↑ Hb A_2 (3.4-7 %), RDW normal
   Normal iron, TIBC & ferritin
3. **β-Thalassemia major:** C/P, ↑↑ Hb F, ↑↑ iron & ferritin
4. **α-Thalassemia trait:** Diagnosis of exclusion, normal Hb electrophoresis
5. **HbH disease (β_4):** mild to moderate hemolytic anemia + splenomegaly + jaundice
6. **Anemia of chronic disease**
7. **Lead poisoning:** Basophilic stippling, ↑↑ blood Lead (> 10 μg/dL), ↑↑ FEP
8. **Atransferrinemia** Iron overload, HSM. Iron is deposited in visceral organs rather than BM
   Rx: blood transfusion + chelating agent + apo-tranferrin
9. **Familial deficient iron absorption** (Parenteral iron)
10. **Sideroblastic anemia** (Sideros = iron)

Definition: Inherited or acquired disorders characterized by **defective heme synthesis**, refractory anemia & ring sideroblast in BM

Ring sideroblast: BM nucleated RBC precursors with retention of iron in the mitochondria in the form of perinuclear iron granules (defective heme synhesis)

Etiology

1. **Congenital sideroblastic anemia** (XLR)
2. **Pearson's syndrome** (Macrocytic)
3. **Acquired:** (Isoniazide, alcohol, Lead, MDS)

Treatment

1. Pyridoxine (B_6)
2. Blood transfusion
3. HSCT

Hemolytic Anemia

Definition

↓↓ RBC life span due to premature destruction.Hemolysis may be extra or intravascular

Etiology

A) **Intracorpuscular (Intrinsic):** Membrane, Enzyme & Hb defects
B) **Extracorpuscular (Extrinsic):** Immune & non-immune causes

Pathophysiology (RBC Destruction & Compensatory mechanisms)

RBC Destruction

- Anemia (↓↓ RBC life span)
- ↑↑ Indirect bilirubin (unconjugated)
- ↑↑ Stercobilinoge & urobilinogen
- ↑↑ Serum iron
- RES hyperplasia
- ↓↓ Haptoglobin (in intravascular)

Compensatory mechanisms

- BM erythroid hyperplasia (6-8 folds)
- ↓↓ M/E ratio (N = 2-4 : 1)
- Expansion of marrow spaces
- ↑↑ Retics
- ↑↑ blood normoblasts
- HSM (extramedullary hemopoiesis)

Clinical picture

A) **Anemia** (Pallor…)

B) **Hemolytic jaundice (3 colors):**

- Eye: jaundice
- Stools: dark
- Urine: normal (darkens on standing, why?)

C) **HSM**

- Destruction of RBCs
- Hemosiderosis (iron overload due to ↑↑ hemolysis, ↑↑ absorption & blood transfusion)
- Extramedullary hematopoiesis
- Anemic HF
- Viral hepatitis

D) **Gall stones** (obstructive jaundice)

E) **Skeletal manifestation** (Mongoloid facies)
Large head, prominent maxillae, protruding central incisors, short broad hands

F) **Manifestations of hemosiderosis**

- Heart: Cardiomyopathy & arrhythmias
- Endocrinal: Pituitary (short stature), Gonads (hypogonadism), DM, Thyroid, hypoparathyroidism...
- Liver cirrhosis
- Skin pigmentation (skin bronzing- bronze diabetes)

G) **Different types of crises**

a. Hemolytic crisis (Aggravation of anemia with deepening of jaundice)
C/P: Fever, bony pains, ↑↑ pallor, ↑↑ jaundice
Lab.: ↑↑ Retics

b. Aplastic crisis (Aggravation of anemia without deepening of jaundice)
C/P: ↑↑ pallor, No ↑↑ jaundice
Lab.: ↓↓ Retics

Parvovirus B_{19}

c. Sequestration crisis (Aggravation of anemia with splenomegaly)
C/P: ↑↑ pallor, splenomegaly (sudden massive pooling of blood in the spleen)

d. Megaloblastic crisis (relative folic acid deficiency)

e. Vaso-occlusive crisis (only in sickle cell anemia)

Investigations

A) For diagnosis of hemolytic anemia

- CBC: anemia (normocytic or microcytic)
- Reticulocytosis
- Blood film:

  Target cells (Hb is concentrated in the center of RBC): Thalassemia, Hb CC
  Sickle cells: Sickle cell disease & trait (spontaneous in disease, induced in trait)
  Spherocytes (small, rounded with lack of central pallor): HS, autoimmune HA
  Elliptocytes (oval cells): in hereditary elliptocytosis
  Stomatocytes (elongated slit replacing the central pallor): in H.stomatocytosis
  Acanthocytes (multiple spiny projections): in abetalipoproteinemia
  Heinz bodies (aggregated denatured Hb): G-6-PD deficiency & unstable Hb
  Howell-Jolly bodies (small basophilic inclusions): asplenia (congenital, surgical or functional hyposplenia Hb SS)

- BM examination (aspirate/ biopsy): hypercellular with ↓↓ or reversed M/E ratio
- Serum: ↑↑ Indirect bilirubin, ↑↑ Iron
- Stools: ↑↑ Stercobilinogen
- Urine: ↑↑ urobilinogen
- ↓↓ RBC life span: 51Cr tagged RBCs
- X-rays: widening of diploic spaces & hair-on-end appearance

B) For differentiation between intra & extravascular hemolysis

- Hemoglobinemia
- Hemoglobinuria
- Hemosiderinuria
- ↓↓ plasma haptoglobin (Haptoglobin combines with free Hb& cleared by RES)
- ↓↓ plasma hemopexin (Hemopexin combines with free heme& cleared by RES)

C) For diagnosis of the cause

- Blood film
- Osmotic fragility (fresh & incubated)
- Acidified glycerol lysis test "AGLT" (fresh & incubated)
- Hb electrophoresis & HPLC
- Sickling test
- Enzyme assay (G-6-PD)
- Coomb's test
- Ham's test (acidified serum lysis test) & Sucrose lysis test

Membrane Defects of RBC

Classification

A) Inherited:

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary pyropoikilicytosis
- Hereditary stomatocytosis

B) Acquired: PNH, abetalipoproteinemia & vitamin E deficiency

Enzymatic Defects of RBC

Classification

A) Glycolysis Pyruvate kinase deficiency
Phosphofructokinase deficiency (hemolysis + myopathy GSD VII)

B) Hexose Monophosphate shunt (Pentose shunt)

- G-6-PD deficiency
- Glutathione & Glutathione reductase deficiency

Hereditary Spherocytosis

Definition

Chronic hemolytic anemia due to hereditary defect of RBC membrane

Etiology

Autosomal dominant (25% new mutation)

Membrane cytoskeletal protein defects involving spectrin, ankyrin or band 3

- Loss of plasticity (↓↓ deformability)
- ↑↑ Na & water permeability → ↑↑ATP use & metabolic work

↑↑ Destruction

Clinical picture (Onset = *may* present in the neonatal period; NJ & anemia)

- May be asymptomatic: Variation in gene expression "penetrance & expressivity"
- General features of chronic hemolytic anemia

Investigations

DD: Immune hemolytic anemia

- General investigations of chronic hemolytic anemia
- CBC: normocytic, spherocytes , ↑↑ MCHC
- Osmotic fragility (RBCs are placed in hypotonic saline): "fresh & incubated"
  Normally, hemolysis starts at 0.45% & is complete at 0.35%
  In HS: hemolysis starts at higher concentrations (i.e., more fragile)
  This finding is accentuated by depriving the cells of glucose "incubated test"
- AGLT (fresh & incubated)
- Membrane cytoskeletal protein analysis (electrophoresis)
- DNA analysis

Treatment

Post splenectomy sepsis

1. Mild cases (Hb > 10 g %): No Rx (just folic acid)
2. Severe cases (Hb < 10 g %): Packed RBC + folic acid ± splenectomy (better > 5yrs)
   Partial splenectomy can be done in children < 5 yrs
   Laparoscopic splenectomy is safe in children
   Selective angio-embolization of splenic artery branches can be done (postoperative pain)
   Precautions with splenectomy: *(see later)*

Splenectomy:
1. Clinical cure (anemia & jaundice)
2. Biochemical & morphological abnormalities are not corrected
3. Spherocytes & osmotic fragility ↑↑

Hereditary Elliptocytosis
Hereditary Pyropoikilocytosis
Hereditary Stomatocytosis

	Elliptocytosis	Pyropoikilocytosis	Stomatocytosis
Etiology	Membrane cytoskeletal protein defects		
C/P	General features of chronic hemolytic anemia (as H.spherocytosis)		
Blood film	Elliptocytes (oval)	Microcytosis, Aniso-Poikilocytosis ↑↑ Thermal instability	Stomatocytes (Elongated slit replacing the central pallor)
Rx	Packed RBC + folic acid ± splenectomy		Splenectomy is not recommended (↑↑ thrombosis)

Paroxysmal Nocturnal Hemoglobinuria

Definition

Chronic hemolytic anemia due to acquired defect of RBC membrane

Etiology (Not inherited)

- ↑↑ **Susceptibility** to damage by **complement** system due to defect in cell membrane proteins that normally inhibit membrane protein
- Deficient proteins include decay-accelerating factor & C8 binding protein
- This abnormality affects marrow stem cells ***(Dyserythropoietic anemia)***, WBC & platelets

Pathophysiology

- Intravascular hemolysis (hemoglobinuria…)
- Nocturnal hemolysis is classic, but chronic hemolysis is more common
- Sleeping (↓↓ RC) ⟶ Mild respiratory acidosis ⟶ ↑↑ complement lysis (hemolysis)
- WBC & PLT are also affected ⟶ release of thrombogenic substances ⟶ thrombosis

Clinical picture

- General features of chronic hemolytic anemia (jaundice, splenomegaly…)
- Dark urine (hemoglobinuria)
- Thrombosis (abdominal pain, stroke…) & infection
- Complications: Aplastic anemia & AML

Investigations

- General investigations of chronic hemolytic anemia
- Intravascular hemolysis *(mention)*
- ↓↓ Retics (Dyserythropoietic anemia)
- ↓↓ WBC & PLT
- ↓↓ serum iron (hemosiderinuria)
- Ham's test (acidified serum lysis test) & Sucrose lysis test [↑↑ complement lysis]
- BM examination (aspirate/ biopsy): Aplastic anemia & AML
- Flow cytometry for CD59

Treatment (No definitive therapy)

- Anemia (folic ± blood transfusion)
- Anticoagulant
- Analgesics for pain
- Iron therapy *(The only hemolytic anemia...)*
- Prednisone & BM transplantation
- Rx of infection, aplastic anemia & AML

Abetalipoproteinemia (Acanthocytosis)

Etiology (AR)

- Absent Apo B-48 (Intestine) ⟶ No chylomicrons ⟶ Fat malabsorption (steatorrhea)
- Absent Apo B-100 (Liver) ⟶ No VLDL & No LDL (↓↓ serum cholesterol & triglycerides)

Clinical picture

- FTT, stearorrhea, rickets
- Neurological (2nd decade): ataxia, PN, deep sensory loss & retinitis pigmentosa
- Hematological: acanthocytes (multiple spiny projections)

Treatment

Medium-chain triglycerides & Vitamin E, A, D, K

Myopathy
Neuropathy
Anemia

Vitamin E Deficiency (tocopherol)

- Vitamin E is **antioxidant.** It prevents peroxidation of RBC membrane lipids (PUFA)
- Deficiency occurs in* preterm & steatorrhea. Oxidants (e.g., iron) will lead to hemolysis
- *Prophylactic* = 0.5-1.5 mg/d *Therapeutic*= 5-30 mg/d [↑↑ PUFA ⟶ ↑↑ Vit.E requirements]

Pyruvate Kinase Deficiency

Etiology (AR)

↓↓ Pyruvate kinase enzyme → ↓↓ ATP production → ↓↓ RBC life span

Clinical picture (Onset = *may* present in the neonatal period; NJ & anemia)

- May be asymptomatic (adulthood)
- General features of CHA (mild pallor& splenomegaly)

Investigations

- General investigations of chronic hemolytic anemia
- ↓↓ Pyruvate kinase enzyme

Treatment

1. Management of NJ
2. Packed RBC
3. Splenectomy (better > 5 yrs)

Glucose-6-Phosphate Dehydrogenase Deficiency

Etiology (XLR)

HMP shunt defect → ↓↓ G-6-PD enzyme → ↓↓ NADPH production → ↓↓ Reduced glutathione → ↓↓ Reduction of H_2O_2 → Hb oxidation, denaturation & precipitation → Heinz bodies → ↑↑ RBC destruction

Physiology

There are > 100 enzyme variants of G6PD

G-6-PD B^+ is the normal enzyme
G-6-PD A^+ is a normal variant
] Polymorphism

G-6-PD B^- (5-40 % activity)
G-6-PD A^- (5-15 % activity)
] Abnormal variants

Hemolysis occurs in patients with G6PD deficiency on exposure to certain drugs (oxidant stress)

Precipitating Factors

1. Fava beans (Mediterranean type; ***favism***)
2. Drugs: **Antibiotics** (Sulfa, chloramphenicol, nitrofurantoin)
   Antimalarial (chloroquine, primaquine), **others** (aspirin, Vit K, methylene blue)
3. Chemicals: benzene & naphthaline
4. Infection: hepatitis & DKA
5. Idiopathic

Clinical picture (Onset = *may* present in the neonatal period; NJ & anemia)

Acute hemolytic crisis: History of exposure… (24-48 hours)
Sudden onset of Pallor, Jaundice (Indirect), Dark urine (Hb)

NB: Chronic hemolytic anemia is a rare presentation of G-6-PD deficiency

Investigations

- Investigation of hemolytic anemia + intravascular hemolysis *(mention)*
- ↓↓ G-6-PD enzyme activity (done 3 weeks after the onset of hemolysis, why??)
- Neonatal screening may be done (Mediterranean)

Treatment

1. Management of NJ
2. Prevention [Avoid…]
3. Packed RBC

DD of Acute hemolytic anemias:

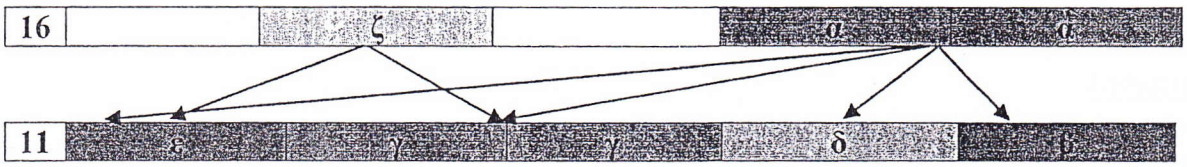
1. G6PD & PK deficiency
2. Hemolytic crisis of CHA
3. AIHA
4. HUS
5. Infection
6. Metabolic (porphyria & Wilson)

Hemoglobin Disorders

Hb is tetramer
There are > 800 Hb variants

Physiology

- Hemoglobin is formed of:
  - **a.** Heme (= iron Fe^{++} protoporphyrin): Not genetically determined
  - **b.** Globin: 4 polypeptide chains (2α + 2 non α); each chain contains a heme group
- Globin part is genetically determined. Two families of genes are responsible:
  - **a. α Gene family** (2α genes& 1 ζ gene) ⟶ 141 aa
  - **b. β Gene family** (β gene, δ gene, 2 γ genes & ε gene) ⟶ 146 aa



Normal Hemoglobin

Normal Hb	Name	Structure
Embryonic Hb	Gower I	2 ζ + 2 ε
	Gower II	2 α + 2 ε
	Portland	2 ζ + 2 γ
Fetal Hb	Hb F	2 α + 2 γ
Adult Hb	HbA	2 α + 2 β
	HbA_2	2 α + 2 δ

- Zeta (ζ) & Epsilon (ε) genes stop working by the 3rd month of pregnancy
- By the 3rd month of pregnancy, Hb F is the major Hb

	At Birth	6-12 months
Hb A	20-30 %	97-98 %
Hb F	70-80 %	0-2 %
$Hb A_2$	-	2- 3.4 %

Diagnosis of Hb disorder:
- Hb electrophoresis
- High performance liquid chromatography (HPLC)

Hb disorders affecting β-chains manifest after 6 months. Why??

Abnormal Hemoglobin

Abnormal Hb	Structure
Hb S	2 α + 2 $\beta^{6\ valine}$
Hb C	2 α + 2 $\beta^{6\ lysine}$
Hb D	Variable
Hb E	2 α + 2 $\beta^{26\ lysine}$
Hb H	4 β
Hb Barts	4 γ
Hb M	↑↑ tendency to oxidation (↑↑ Met Hb formation)
Hb Lepore	Fusion of β & δ genes
Hb constant spring	↑↑ α chain by extra 31 aa (sense mutation)

- During fetal life& early childhood, HbF & HbA (β & γ) are inversely proportionate
- 3 months before birth, ↓↓ γ &↑↑β synthesis *(Hb switch)*

↑↑ HbF:
1. Thalassemia (major & trait)
2. HPFH
3. B chain hemoglobinopathy (sickle…)
4. Hematologic stress: aplastic anemia, HA, Diamond-Blackfan $, leukemia
5. r-HuEPO therapy

Classification of Hb Disorders

A) Qualitative (Hemoglobinopathy) [Structural defects] Hb S, Hb C, Hb M…
- **a. Sickle cell disease & sickle cell trait**
- **b. HbC, HbD, HbE**
- **c. Unstable Hb**

B) Quantitative [↓↓ formation of α or β chains]
- **a. β Thalassemia** [↓↓ formation of β chains]
- **b. α Thalassemia** [↓↓ formation of α chains]
- **c. Hereditary persistence of fetal Hb (HPFH):** failure of switch from γ to β chain

Sickle Cell Anemia

(Homozygous Hb SS)

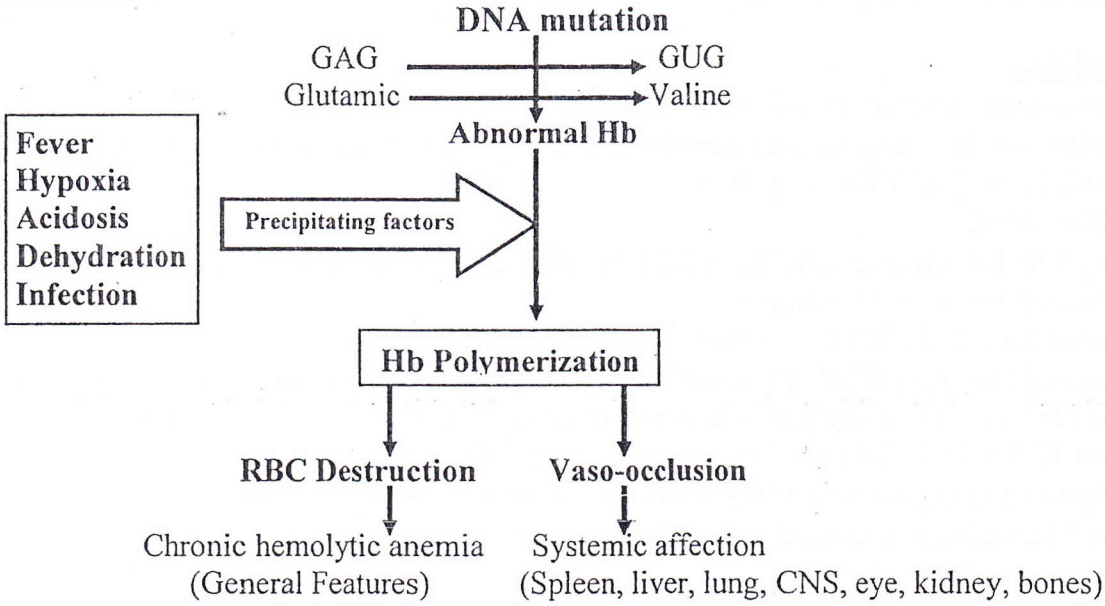
Definition

It is chronic hemolytic anemia due to homozygous occurrence of sickle gene

Etiology& Genetics *(Incomplete AD)*

- Point mutation in **both** β-genes (i.e., **homozygous**)
- Abnormal structure of β-chains (valine replaces glutamic acid the 6th aa from amino end)
- Both parents are carriers (sickle cell trait)
- Hb electrophoresis = No HbA, HbS 80-95%, HbF 2-20%

Pathophysiology



Clinical picture (Onset = 2nd half of the 1st year)

Autosplenectomy

1. General features of CHA (No splenomegaly)
2. Vaso-occlusive crisis
3. Sequestration crisis
4. Aplastic crisis
5. Hyperhemolytic crisis (G6PD deficiency is a possible cause)
6. Organ dysfunction
   - ☒ Liver: hepatomegaly, Gall stones, transfusion-related hepatitis& cirrhosis
   - ☒ Eye: retinopathy, blindness
   - ☒ Skin: leg ulcers
   - ☒ Kidney:
     - Hypothenuria (urine concentration defect due to affection of vasa recta)
     - Acquired nephrogenic DI & RTA (due to interstitial fibrosis)
     - Hematuria (due to papillary necrosis) **Rx**: Aggressive IV hydration
     - Proteinuria & nephrotic $: **Rx**: ACE inhibitors (captopril)
     - CRF (due to chronic interstitial nephritis & focal scarring)
   - ☒ Cardiomyopathy: (due to anemia, VOC & hemosiderosis)
   - ☒ Lung: ACS, pulmonary fibrosis, pulmonary hypertension & cor-pulmonale
   - ☒ Spleen (functional hyposplenism):↑↑risk of infection 300 folds (Max.in 1st 5yrs)

   Organisms: Pneumococci, Haemophilus influenza, Meningococci& Salmonella
   - ☒ CNS: neuropsychological deficit (IQ, speech, seizures & motor deficits)

Stroke may be:
1. **Overt** (C/P)
2. **Silent** (MRI)

Clinical picture of vaso-occlusive crisis

1. Hand-foot syndrome (Acute sickle dactylitis): Painful swelling usually < 5 yrs
2. Bone crisis: Fever, pain, tenderness& swelling usually affecting multiple sites [↓↓ Uptake by ***bone scan***. DD: Osteomyelitis]
3. Abdominal crisis: due to affection of mesenteric vessels [DD: Acute abdomen]
4. Intra-hepatic crisis (Hepatic sequestration): Sudden painful liver enlargement with ↑↑ bilirubin& liver enzymes [DD: Acute hepatitis]
5. Acute chest syndrome (ACS): Chest pain, dyspnea & fever [normal CXR & abnormal ***V/Q scan***. DD: Pneumonia]
6. CNS crisis: Convulsions, motor deficits, meningeal signs, stroke & blindness
7. Hematuria: mild& painless (due to papillary necrosis)
8. Priapism (due to papillary necrosis)

Investigations

- General investigations of chronic hemolytic anemia
- CBC: Normocytic normochromic anemia (mid to moderate), sickle cells & Howell-Jolly bodies, ↑↑ WBC, ↑↑ PNL, ↑↑ Retics
- ↓↓ ESR (sickling)
- Sickling test: Induction of sickling of RBC by deoxygenation or addition of reducing substances (Na metabisulphite)
- Hb electrophoresis & HPLC: No HbA, HbS 80-95%, HbF 2-20%
- Transcranial Doppler (TCD): ↑↑ blood flow velocity in the cerebral arteries (> 200cm/sec) is associated with ↑↑ risk of stroke & is an indication of chronic transfusion therapy to maintain HbS < 30 %. TCD is done yearly starting at the age of 2-3 years
- Investigations of organ dysfunction: bone scan, lung scan, echo-, KFTs, LFTs…
- Neonatal screening & antenatal diagnosis (using restriction enzymes e.g., Mst II…)

Treatment

1. Parent **education** (temperature, palpation of spleen, symptoms of sickle cell disease)
2. Folic acid
3. **Vaccination**: HBV, Hib, meningococcal vaccines
   PCV (pneumococcal conjugate v): 2, 4, 6& 15 months (routine in USA)
   PPV (pneumococcal polysaccharide v): at 2 yrs of age
4. Penicillin **prophylaxis** starting at the age of 2 months;
   Children < 3 yrs 125 mg twice daily
   Children > 3 yrs 250 mg twice daily
   Allergic patients ⟶ Erythromycin
   } Continue till the age of 5 yrs
5. Patients with **fever**
   - Thorough examination
   - Investigations: (CBC, CXR, blood& urine cultures)
   - All patients <5 yrs with documented fever should be admitted
   - Ceftriaxone (75 mg/Kg/d) is the drug of choice
6. Aplastic & hyperhemolytic **crisis**: Blood transfusion
7. Sequestration crisis:
   - Blood transfusion ± exchange transfusion
   - Splenectomy in recurrent/ severe cases
8. Acute chest $ (**ACS**):
   - Oxygenation & Respiratory support
   - Blood transfusion (Do Not ↑↑ Hb > 11 g %)
   - Exchange transfusion (if hypoxemia, marked RD or Rt sided HF) to↓↓ HbS < 30%
   - Pain control
   - Antibiotics (e.g., Ceftriaxone)

9. Management of neurological complications (stroke)
   - Oxygenation
   - Blood transfusion (Do Not ↑↑ Hb > 11 g%)
   - Exchange transfusion (↓↓ HbS < 30%)
   - Secondary prevention: chronic transfusion therapy

10. Drug therapy (Hydroxyurea):
    Mechanism: ↑↑ HbF formation
    Side effects: myelosuppression, renal impairment, hair loss& GIT disturbances
    Monitoring: monthly CBC, MCV, LFTs, HbF
11. Bone marrow transplantation (from HLA matched sibling)

Treatment of vaso-occlusive crisis

1. Hydration (1.5 times maintenance)
2. Analgesia

- Paracetamol (15 mg/Kg/dose)
- Aspirin (15 mg/Kg/dose)
- Ibubrufen (15 mg/Kg/dose)
- Morphine (0.15 mg/Kg/dose) IM
- Meperidine (1.5 mg/Kg/dose) IM
- Codeine (0.75 mg/Kg/dose) PO

3. Blood transfusion/ exchange transfusion

Indications of blood transfusion/ exchange transfusion:
1. Anemia
2. Refractory painful crisis
3. Splenic sequestration
4. Stroke
5. Acute chest $
6. Elective surgery (anesthesia)
7. Priapism
8. Pregnancy (latter part)

Aim:
To ↓↓ HbS < 30 %

Hemoglobin S-βThalassemia:
Genetics:
The presence of genes for HbS& thalassemia
1. HbS-B^+: HbS (60-80%) + HbA(<30%) + mild ↑↑ HbF & HbA_2
2. HbS-B^0: HbS + No HbA (exactly as SS)

	HbSS	HbS-B^0
MCV	Normocytic	Microcytic
Parents	Both are sickle cell trait	HbAS Thalassem. trait

C/P: Variable
VOC + splenomegaly

Sickle cell syndromes:

Sickle cell anemia (SS)	S-β^0Thalassemia
Sickle cell trait (AS)	S-β^+Thalassemia
Hemoglobin SC	S-HPFH

Sickle cell disease:
Sickle cell anemia (SS)
Compound heterozygous e.g,
S-β^+Thalassemia, Hb SC, S-HPFH

Sickle Cell Trait

(Hb AS)

Genetics

Heterozygous mutation of β gene (valine replaces glutamic acid…)
Hb electrophoresis: HbA 60 % + HbS 40 % *(AS pattern)*

Clinical picture

- Asymptomatic under normal conditions
- Sudden death may occur during vigorous exercises
- VOC can occur with hypoxemia (shock, flying, high altitudes & GA)
- Genetic counseling (when both parents are trait, there is 25% risk of sickle cell anemia)

Treatment No restriction of activities

Thalassemia Syndromes

Thalassa = sea

Definition

Chronic hemolytic anemia due to inherited quantitative defect of Hb caused by:

a. Deficient synthesis of one of the globin chains (α or β chains)

b. The **imbalanced** chain production leads to **precipitation** of globin chains in:

- Bone marrow RBC precursors: Dyserythropoietic anemia
- Circulating RBCs: Hemolytic anemia (Intra-corpuscular- extravascular)

Classification& Genetics

A) β Thalassemia [↓↓ formation of β chains]

β^0 = absent β-chain synthesis β^+ = reduced β-chain synthesis

Genetics:

- ***Point mutation:*** affecting transcription, mRNA splicing or translation
- ***Deletion:*** of β gene
- ***Hb Lepore:*** fusion between β and δ genes (unequal crossing-over)

B) α Thalassemia [↓↓ formation of α chains]

Genetics:

- ***Deletion:*** of ≥ one of the 4 α genes (silent carrier, trait, HbH, hydrops fetalis)
- ***Chain terminator defect:*** sense mutation of stop codon leading to α chain with an extra 31 aa (Hb Constant Spring)

C) Hereditary persistence of fetal Hb (HPFH): failure of switch from γ to β chain

α-Thalassemias

Definition

Deficient synthesis of α chain due to **deletion** or mutation of α gene (Hb Constant Spring)
Hemolysis is caused by precipitation of free β & γ chains

Classification

According to the number of deleted genes:

Syndrome	# Gene	Genotype	Hematological	C/P	Hb
α-Silent carrier	1	- α/ α α	Normal	Normal	Neonate: Hb Barts (1-2 %)
α-Thalassemia trait	2	- α/- α or --/ α α	Microcytosis Hypochromia	Normal Mild anemia	Neonate: Hb Barts (5-10 %)
HbH disease	3	- α/ - -		Mild H. anemia	Neonate: Hb Barts (20-30 %)
Hydrops fetalis	4	- -/ - -	Anisocytosis Poikilocytosis	Death IU or Early neonatal	Neonate: Hb Barts (80-90 %)

HbH disease: mild to moderate hemolytic anemia + splenomegaly + jaundice + Transfusion is usually not required. Hydrops fetalis: transfusion + BM transplantation (the only cure)

Hereditary Persistence of Fetal Hb

Definition

Failure of switch from γ to β chain commonly caused by deletion of β and δ genes

Clinical Picture

Homozygous: mild anemia + microcytosis + HbF (100 %)
Heterozygous: HbF (20-40 %)
Sickle-HPFH: **mild** manifestation (HbF prevents sickling)

β-Thalassemia Syndromes

Definition

Deficient synthesis of β chain due to mutation or deletion of β gene. It may be β^0 or β^+.
Hemolysis is caused by precipitation of free α-chain.

Concomitant α-thalassemia ameliorates the C/P of β-thalassemia

Classification

1. **Homozygous β Thalassemia** [Thalassemia major; $\beta^0\ \beta^0$ or $\beta^+\ \beta^+$]
2. **Heterozygous β Thalassemia** [Thalassemia trait; $\beta\ \beta^0$ or $\beta\ \beta^+$]
3. **Special phenotypic type** [Thalassemia Intermedia]

Thalassemia Trait (Thalassemia minor)

Genetics

Heterozygous β^0 or β^+

Clinical picture

Asymptomatic (normal examination). Discovered accidentally

Investigations

Mild microcytic hypochromic anemia (RDW normal or ↑↑)
Normal iron, TIBC & ferritin
↑↑ **Hb A_2** (3.4-7 %) & mild ↑↑ HbF (2-6 %)

Importance

- DD of iron deficiency anemia
- Genetic counseling (when both parents are trait, there is 25% risk of thalassemia major)

Thalassemia Major (Cooley's anemia)

Genetics

Homozygous β^0 or β^+

Clinical picture (Onset = 2nd half of the 1st year)

Hb A is *absent* in β^0 thalassemia & *decreased* in β^+ thalassemia

General features of CHA *(mention)*

Investigations

- General investigations of chronic hemolytic anemia (Hb < 5 g %)
- Assessment of iron overload: serum ferritin, specialized MRI, liver biopsy
- Hb electrophoresis & HPLC: HbF > 70 %, normal Hb A_2 and Hb A is *absent* or *decreased*

Thalassemia Intermedia

Genetics

Homozygous β^0 or β^+ (?? modified by associated α-thalassemia or HPFH)

Clinical picture (General features of thalassemia), but…

- Onset: after 2 years of age
- Hb level: maintained between 6-8 g %
- Do not require regular blood transfusion
- Extramedullary hematopoiesis can occur in the vertebral canal (neurologic symptoms)

Investigations General investigations of chronic hemolytic anemia

Treatment

1. Transfusion: Controversial
2. Local radiation therapy for vertebral canal hematopoiesis (↓↓ erythropoiesis)
3. Splenectomy may be needed
4. L-carnitine & Hydroxy urea

Treatment of Thalassemia (& CHA)

A) Blood transfusion

Target: Post transfusion Hb = 9.5 g%

Hypertransfusion (Hb > 10g %) & supertransfusion (Hb > 12g %) should be avoided, why?

Value:

- Improve activity& growth
- Improve cardiac function
- # BM expansion (cosmetic)
- ↓↓ GIT iron absorption

Amount: 10-20 ml/ Kg every 4-5 weeks

Type of blood:

- Fresh (? Neocyte)
- Filtered (Leukocyte depleted)
- Washed (↓↓ plasma proteins)
- CMV free
- Irradiated (if BM transplantation)
- ?? Paired donor & recipient
- Phenotypically matched (including minor blood groups; kell…)

RBC phenotype should be obtained at diagnosis

Neocyte transfusion: young RBC with ↑↑ life span ⟶ ↓↓ frequency of blood transfusion

Paired donor & recipient programs: are used in some centers (↓↓ Risk of sensitization)

Causes of ↑↑ Frequency of transfusion:

- Hypersplenism
- isoimmunization
- Folic acid deficiency

Complications *(mention)*

B) Iron chelating therapy

Indications: when serum ferritin > 1000 ng/ml, usually > 4-5 years

1. Deferoxamine (Desferal)

Dose: 40-60 mg/Kg/day using portable electronic SC pump over 10-12 hrs/day for 5-6 days/week. IV Deferoxamine may be used in severe cases

Side effects:

- Ototoxicity
- ↓↓ Visual field & acuity
- Local: pruritis, swelling & rash

2. Deferiprone (L-1): Oral chelating agent

Side effects: Neutropenia

3. ICL 670: Oral chelating agent

Causes of osteoporosis:

- BM expansion (pressure)
- Deficiency of sex hormones
- Nutritional deficiency

C) Splenectomy

Indications:

- Massive splenomegaly
- ↑↑ Frequency of transfusion (hypersplenism): > 240 ml/Kg/year

Vaccination: Before splenectomy (Hib, meningococcal & pneumococcal vaccines)

Penicillin prophylaxis: After splenectomy

Methods:

- Total splenectomy
- Partial splenectomy
- Laparoscopic splenectomy
- Angio-embolization

D) Folic acid & Vitamin D & Calcium

E) Vaccination

F) Diet Avoid iron rich food + "cup of tea" with each meal to ↓↓ iron absorption

G) Rx of osteoporosis sex hormone replacement (adolescence),calcitonin & bisphosphonate

H) BM Transplantation from HLA matched sibling, successful specially in children < 15 yrs without hepatomegaly, iron overload and with previous few transfusions

I) Hydroxyurea: ↑↑ HbF

J) Gene therapy: activation of γ gene ⟶ ↑↑ HbF

Complications of Blood Transfusion

A) Acute Transfusion Reactions

1. Acute hemolytic reaction

- **Cause:** Incompatible blood transfusion "Clerical error"
- **Clinical Picture:** Fever, chest pain, back pain, RD, tachycardia, hypotension, DIC
- **Prevention:** Proper cross-matching
- **Treatment:**
  - DC transfusion
  - IV fluids: Normal saline or lactated Ringer's + Urine alkalinisation
  - Diuretics (furosemide)
  - Dopamine (renal dose?)
  - Dialysis

Filtered blood: leukocyte depleted

2. Febrile non-hemolytic transfusion reaction

- **Cause:** Alloimmunization to antigens on WBCs & platelets (release of cytokines)
- **Clinical Picture:** Fever + chills (in multi-transfused patients)
- **Prevention:** Use of filtered blood [± Premedication with antipyretics & hydrocortisone]
- **Treatment:**
  - DC transfusion (DD: hemolytic reaction)
  - Antipyretics & hydrocortisone

3. Allergic reaction

- **Cause:** Reaction to donor's plasma proteins
- **Clinical Picture:** Erythema, urticaria, laryngospasm, hypotension, anaphylaxis
- **Prevention:** Use of washed blood
- **Treatment:**
  - Mild cases: antihistaminics (Diphenhydramine) & continue blood transfusion
  - Anaphylaxis: Adrenaline & steroids (hydrocortisone)

4. Bacterial contamination

- **Cause:** Bacterial contamination
- **Clinical Picture:** Fever, hypotension, shock, DIC, sepsis
- **Prevention:** Proper sterilization & avoid room temperature storage
- **Treatment:** Broad spectrum antibiotics

B) Other adverse effects of blood transfusion

1. **Delayed hemolytic reaction**
2. **Isosensitization to RBC, WBC or platelet antigens**
3. **Bleeding tendency** (↓↓ Platelet & ↓↓ Coagulation factors)
4. **Graft versus host disease**
5. **Disease transmission**
   - Viral: HBV, HCV, HIV, CMV, EBV
   - Bacterial: Syphilis, bacterial sepsis
   - Protozoa: toxoplasmosis, malaria
6. **Volume overload:** HF
7. **Hypothermia:** Massive blood transfusion
8. **Hypocalcemia:** Citrate toxicity
9. **Hyperkalemia:** Old blood
10. **Iron overload (hemosiderosis)**

Blood Products

Whole blood, packed RBC, FFP, cryoprecipitate, platelets, granulocytes, coagulation factors, VIC albumin

Iron Overload Disorders

(Hemochromatosis)

Definition

Excessive deposition of hemosiderin in the tissues;

- RES: hemosiderosis (tissue damage is less serious)
- Parenchymal cells: hemochromatosis

Classification

Primary (Hereditary)	Secondary (Acquired) "C.H.A."
Hereditary hemochromatosis (adult)	Iron overload occurs due to: ▪ ↑↑ Hemolysis ▪ Blood transfusion ▪ ↑↑ GIT iron absorption
Juvenile hemochromatosis	
Neonatal Iron Storage Disease (NISD)	
Atransferrinemia	

A) Hereditary hemochromatosis (HH)

Etiology: AR

Pathogenesis: ↑↑ GIT iron absorption (up to 20-40 %)

C/P: Age = 40-60 years

Liver cirrhosis, skin pigmentation (bronzing) & DM

Investigation: ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

Rx: ↓↓ dietary iron

Repeated venesection

B) Juvenile hemochromatosis

Etiology: Not genetic

Pathogenesis: Iron deposition mainly in heart& pancreas

C/P: Cardiomyopathy, arrhythmias& DM

Investigation: ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

Rx: ↓↓ dietary iron

Repeated venesection

C) Neonatal Iron storage Disease (NISD)

Etiology: AR

Pathogenesis: Iron deposition in liver, heart& pancreas

C/P: Age = 1st week of life (usually preterm or SGA)

Hepatomegaly, *cholestasis* & cirrhosis

Investigation: ↑↑ serum iron, ↑↑ serum ferritin, ↑↑ transferrin saturation

↓↓ albumin, ↓↓ prothrombin concentration, ↓↓ glucose

MRI

Liver biopsy: cirrhosis with ↑↑ hemosiderin

Buccal biopsy: ↑↑ hemosiderin

Rx: Anti-oxidants + iron chelating agents

Liver transplantation

Prognosis: fulminant liver disease

D) Atransferrinemia

Iron overload, HSM. Iron is deposited in visceral organs rather than BM

Microcytic hypochromic anemia

Rx: blood transfusion + chelating agent + apo-tranferrin

Extracorpuscular Hemolytic Anemia

Definition

↓↓ RBC life span due to premature destruction caused by extra-corpuscular factors

Classification

1. **Immune hemolytic anemia**
   - **a. Active:** Autoimmune hemolytic anemia (auto-Ab are formed by the patient)
   - **b. Passively acquired antibodies:** Isoimmune hemolytic anemia
     Hemolytic disease of the newborn (Rh,ABO,minor) & mismatched blood transfusion
2. **Nonimmune hemolytic anemia:** MAHA, infections, hypersplenism,Wilson, chemicals

Autoimmune Hemolytic Anemia

Definition

↓↓ RBC life span due to premature destruction by auto-Ab formed by the patient

Classification& Clinical Picture

AIH due to warm antibodies	AIH due to cold antibodies
Etiology **1. Primary (Idiopathic)*** **2. Secondary:** Collagen-vascular diseases(SLE,U.colitis) Malignancy (lymphoma) Infections (CMV) **3. Drugs** *(3 mechanisms)* Hapten (peniciliin) Ternary complex (quinine) Induction of auto-Ab (α-methyldopa)	**1. Primary (Idiopathic)** **(= Primary cold agglutinin disease)** **2. Secondary** **(= Secondary cold agglutinin disease)** Malignancy (lymphoproliferative) Infections (mycoplasma, EBV) **3. Paroxysmal cold hemoglobinuria** Due to the presence of cold **IgG** (not IgM) • Primary • Secondary (viral infection & syphilis)
Autoantibodies • IgG (monomer) • Active between 35-40° C • Do not require complement for activity • Do not cause agglutination in vitro	• IgM (pentamer) • Active < 37° C (best at 0- 4° C) • Require complement for activity • Cause agglutination in vitro
Clinical picture **A) Acute AIHA:** Age= 2-12 years Acute onset of pallor, jaundice & Hb-uria Marked splenomegaly Good response to steroid Full recovery within 3-6 months **B) Chronic AIHA:** Age >12 years Gradual onset of pallor, jaundice Mild splenomegaly Variable response to steroid Underlying cause is usually present	**A) Cold agglutinin disease (1ry&2ry)** Hemolysis & Hb-uria follow cold exposure Splenomegaly **Rx:** Avoid cold + Rx of the cause Immunosuppression& plasmapharesis Rituximab (monoclonal Ab) Poor response to steroid **B) Paroxysmal cold hemoglobinuria** Age >12 years Gradual onset of pallor, jaundice Mild splenomegaly

Investigations

- General investigations of chronic hemolytic anemia
- CBC: Normocytic normochromic anemia with ↑↑ Retics (reticulocytosis)
- ↓↓ Platelet in secondary cases (SLE) & Evans $ (AIHA & thrombocytopenia)
- BM examination (aspirate/ biopsy): hypercellular with ↓↓ or reversed M/E ratio
- Serum: ↑↑ Indirect bilirubin, ↑↑ iron
- Stools: ↑↑ Stercobilinogen
- Urine: ↑↑ Urobilinogen
- ↓↓ RBC life span: ^{51}Cr tagged RBCs
- Coombs test (for detection of auto-Ab): Most important
  - **a.** *Direct:* detects Antibodies coating RBCs [at least 250-500 Ab should be present/cell]
  - **b.** *Indirect:* detects Antibodies circulating in the patient's serum

Treatment

1. Rx of the cause, avoid drugs… and avoid cold…
2. Blood transfusion
   - Transient benefit: Do not give unless indicated (severe anemia, anemic HF)
   - Difficult to get compatible blood: give *the least incompatible* blood
   - Warming of blood: in AIHA due to cold reacting Ab
3. Steroids: IV methylprednisolone (Solu-medrol) 10-30 mg/Kg/day in acute cases
   Oral prednisone 2 mg/Kg/day (till recovery with gradual tapering)
4. IVIG: block splenic Fc receptors
5. Plasmapharesis: removal of auto-Ab
6. Immunosuppressive
7. Rituximab (anti-CD20): inhibits B-lymphocytes ⟶ plasma cells ⟶ Ab

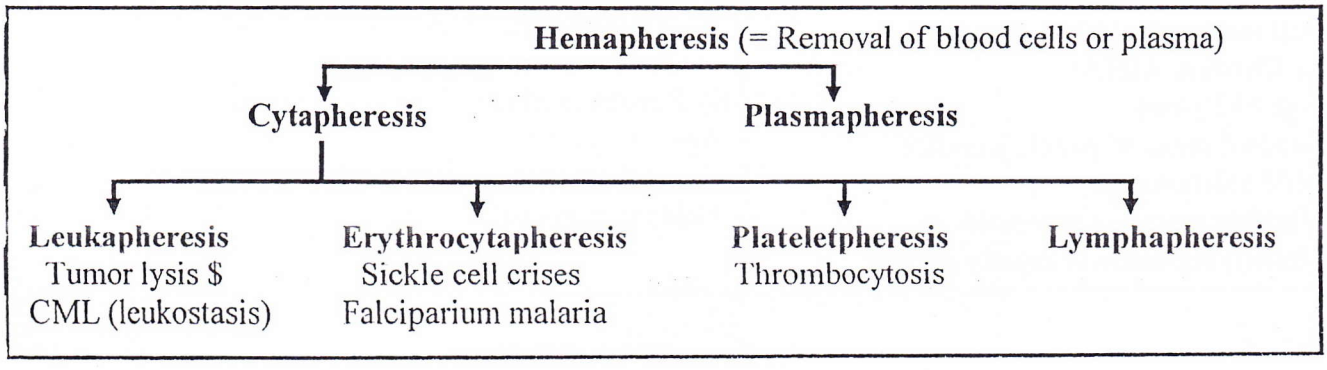
Indications of plasmapheresis:

1. Autoimmune hemolytic anemia
2. Acute ITP
3. Incompatible blood transfusion
4. Guillain-Barre syndrome
5. Myasthenia gravis
6. HUS
7. TTP
8. RPGN
9. SLE (Lupus nephritis)
10. Goodpasture disease
11. Hyperlipidemia
12. Maternal Ab mediated diseases (Rh...)
13. Intoxication

Replacement fluid: Albumin 5%, FFP or NS

Indications of exchange transfusion:

1. Sickle cell anemia. When?
2. Cyanotic CHD
3. Polycythemia
4. Hemolytic disease of the NB
5. Neonatal sepsis
6. DIC
7. Neonatal RD (maternal drugs or GA)
8. Hypermagnesemia
9. Inborn errors of metabolism



Pancytopenia

Definition

↓↓ of the 3 blood cells RBC, WBC & platelets

Etiology

A) Aplastic anemia

a. Constitutional: [= Inherited BM failure syndromes]

Fanconi anemia — Dyskeratosis congenita,
Shwachmann-Diamond$ — Amegakaryocytic thrombocytopenia

b. Acquired

B) BM infiltration

- Malignancy: Leukemia
- Osteopetrosis
- Myelofibrosis

C) Megaloblastic anemia

D) ↑↑ Peripheral destruction: Hypersplenism, PNH & Immune (SLE)

Clinical picture

- Anemia: Pallor
- Thrombocytopenia: Bleeding
- Leucopenia: Infection (fever)

Constitutional Aplastic Anemia

Definition

↓↓ of the 3 blood cells RBC, WBC & platelets due to an inherited ~~etiology~~

A) Fanconi anemia** (AR)

- Short stature
- Microcephaly, Microphthalmia
- Skin pigmentation (café-au-lait patches)
- Mental retardation & hyperreflexia
- Thumb anomalies (triphalangeal or hypoplastic)
- Radius anomalies
- Renal anomalies (ectopic, dysplasia or horseshoe)
- Pancytopenia (mean age = 6-8 yrs)
- ↑↑ risk of malignancy (leukemia)

Investigation:

1. CBC: Pancytopenia, ↑↑ MCV, ↑↑ HbF
2. BM examination (aspirate/ biopsy): Hyporcellular
3. Chromosomal breakage study
4. Others: Skeletal survey, renal assessment…

DD of café-au-lait spots:

1. Neurofibromatosis
2. Fanconi anemia
3. McCune Albright $
4. Chediak-Higashi $
5. Ataxia telangiectasia
6. Bloom $
7. Tuberous sclerosis

Inherited causes of chromosomal breakage:

1. Fanconi anemia
2. Ataxia telangiectasia
3. Bloom syndrome
4. Xeroderma pigmentosa

B) Dyskeratosis congenita (AR)

- Short stature
- Mental retardation
- Skin pigmentation
- Ectodermal dysplasia (Skin pigmentation, nail dystrophy & mucosal leukoplakia)
- Ocular (epiphora & blepharitis)

C) Amegakaryocytic thrombocytopenia (AR)

D) Shwachmann-Diamond $ (Neutropenia with pancreatic insufficiency) (AR)

- Metaphyseal chondrodysplasia (short stature)
- Mental retardation
- Pancreatic insufficiency ⟶ Malabsorption (steatorrhea) ⟶ FTT & short stature
- Neutropenia ⟶ pyogenic infection ± Anemia & thrombocytopenia

Pathology

1. Pancreas: Atrophy of acini with replacement by **fat** with no fibrosis (Normal islets)
2. BM examination (aspirate/ biopsy): hyporcellular

Investigation

1. Fat malabsorption
2. CBC: Neutropenia ± anemia & thrombocytopenia
3. Sweat chloride test: normal

DD

1. Cystic fibrosis: pancreatic acinar **fibrosis**, ↑↑ sweat chloride
2. Pearson's $: acinar *fibrosis*, vacuolization of BM precursors & ringed sideroblasts

Treatment

1. Pancreatic enzyme replacement
2. Antibiotics
3. GM-CSF or G-CSF
4. BMT

E) Other genetic syndromes: Down syndrome, Seckel syndrome

Seckel syndrome
- Bird-headed dwarfism
- Hypoplastic face
- Prominent nose
- Low-set ears

Acquired Aplastic Anemia

Etiology

1. Idiopathic (most common)**
2. Irradiation
3. Infection (viruses): CMV, EBV, HBV, HCV, HIV& Parvovirus B_{19}
4. Immune: immunodeficiency (Parvovirus B_{19})
5. Drugs
   a. Predictable: Cytotoxic (chlorambucil), benzene
   b. Idiosyncrasy: *Antibiotics* (chloramphenicol)
      Antiepileptics (phenytoin)
      Anti-thyroid (methimazole, PTU)
6. PNH
7. Pregnancy

Pathogenesis

1. Direct toxic effect on BM precursors
2. Immune-mediated reaction against BM precursors (Cell-mediated) "↑↑ Cytokines"

Clinical picture (Pancytopenia)

- Anemia: Pallor
- Thrombocytopenia: Bleeding
- Leucopenia: Infection (fever)

Severe Aplastic anemia =
BM aplasia or hypoplasia + 2 of:
- ANC < 500/mm^3
- PLT < 20.000/mm^3
- Retics < 1%

Investigations

1. CBC: pancytopenia, ↑↑ MCV, ↑↑ HbF
2. BM examination (aspirate/ biopsy): hyporcellular
3. Investigation of the cause (hepatitis, PNH…)

Treatment

1. Isolation (if ANC < 500 mm^3)
2. Diet: high protein & multivitamins
3. Blood transfusion (better from parents or siblings to ↓↓ risk of alloimmunization)
   - Packed RBC: if Hb < 7-9 g % (use irradiated & leukocyte depleted blood)
   - Granulocyte transfusion: for prophylaxis (if ANC < 500/mm^3) & for Rx of sepsis
   - Platelet transfusion: for prophylaxis (if PLT < 10.000-20.000/mm^3) & for Rx of Hge
4. Antibiotics: for prophylaxis (SMZ-TMP) & for Rx of infection
5. Rx of acquired aplastic anemia
   ☒ Immunosuppresion
      - Anti-thymocyte globulin (ATG)
      - Cyclosporine
      - Methylprednisolone
   ☒ GM-CSF or G-CSF (Granulocyte-macrophage colony stimulating factor):
   Used to ↑↑ granulopoiesis in patients with severe neutropenia
   ☒ BMT (HLA-matched donor)
6. Rx of constitutional aplastic anemia (Fanconi anemia)
   ☒ Androgen ± steroids
   [Side effects of androgens: hirsutism, acne & hepatotoxicity]
   ☒ GM-CSF or G-CSF
   ☒ BMT (HLA matched donor)

Prognosis

- Mortality in untreated patients = 75% [Hge & infection]
- Long –term survival = 90% in patients with successful BMT

Management of Neutopenic Fever

Definition

- **Fever** > 38.5°C or 3 elevations > 38°C during 24 hour period
- **Neutropenia** < 500/ mm^3

Common Organisms

- Bacteria: G +ve (Staph.aureus, CONS, Streptococci)
  G -ve (Pseudomonas)
- Fungal: Candida & Apergillus
- Viral: CMV& VZV

Management

1. Hospital admission& isolation
2. Thorough examination
3. Appropriate cultures & CXR
4. First line antibiotics:

   Imipenem (Tienam) / Meropenem (Meronam) + Ceftazidime (Fortum) / Cefepime (Maxipime) ± Aminoglycoside
5. Catheter related infection: Vancomycin
6. Perirectal infection: add clindamycin or metronidazle (anaerobes)
7. Persistent fever > one week: Antifungal (Amphotericin B)
8. Total duration of antibiotic therapy: till resolution of infection (usually 10-14 days)

Disorders of Leukocytes

Leukocytosis

Total WBC count 2 SD above the mean for age

Leukopenia

Total WBC count < 4.000/ mm^3

Neutrophils

Development

Myeloblast
↓
Promyelocyte
↓
Myelocyte
↓
Metamyelocyte
↓
Band
↓
Segmented

Functions

Chemotaxis (LPS, C5a)
↓
Attachment (opsonization)
↓
Ingestion (phagosome → phagolysosome)
↓
Digestion (Intracellular killing)
- O_2-dependent (superoxide O^-_2,H_2O_2, hypochlorous HOCl)
- O_2-independent (proteolytic & hydrolytic enzymes)

Neutrophilia

Definition

Absolute neutrophil count > 12.000/ mm^3 in the 1st day of life
> 8.000/ mm^3 in adults

Etiology

1. Infection (Bacterial): pyogenic infections
2. Inflammation: JRA, IBD, Kawasaki
3. Hemorrhage
4. Hemolysis
5. Trauma & surgery
6. Tissue injury (burns)
7. Malignancy
8. Metabolic: DKA, CRF
9. Exercise
10. Epinephrine
11. Leukocyte adhesion deficiency (LAD)
12. Leukemoid reaction: (= TLC > 50.000/ mm^3)
13. Drugs: GM-CSF, G-CSF & steroids
14. AD form of hereditary neutrophilia
15. Postsplectomy (& asplenia)

Shift to the left:
↑↑ Proportion of band (staff)
Band / (Band + Segmented) > 0.2
Shift to the right:
Hypersegmentation (↓↓ folic & B_{12})

Leukemoid reaction
- WBC > 50.000/ mm^3
- ↑↑ Neutrophils
- ↑↑ Activity of WBC ALP

Neutropenia

Definition

Absolute neutrophil count < 1.500/ mm^3

- ☒ Mild neutropenia: ANC 1000-1500/ mm^3
- ☒ Moderate neutropenia: ANC 500-1000/ mm^3
- ☒ Severe neutropenia: ANC < 500/ mm^3

Etiology

1. Intrinsic disorders (BM myeloid cells)
2. Extrinsic disorders

Clinical picture

- Fever, oral ulcers, stomatitis, gingivitis, pharyngitis, sinusitis, OM, cellulites & colitis
- Pneumonia, lung abscess, liver abscess & sepsis
- Mild symptoms & signs of inflammation. Why?

Investigations

- CBC, ANC, Anti-neutrophil Ab, BM study
- F/U of ANC to exclude cyclic neutropenia

Treatment

1. Management of infections
2. Granulocyte transfusion, GM-CSF or G-CSF
3. BMT
4. Specific Rx e.g., hypoglycemia, androgens, IVIG, pancreatic enzyme replacement

Intrinsic disorders causing Neutropenia

	Defect	C/P	Lab
Cyclic neutropenia (AD)	Periodic regular oscillation of ANC (≈21 days)	Fever, oral ulcers, stomatitis, pharyngitis, sinusitis, OM, pneumonia, sepsis	↓↓ ANC during attacks
Severe congenital neutropenia (Kostmann $)	Arrest of maturation at promyelocytic stage (sporadic)	- Onset = 1st few months Recurrent pyogenic infections (pneumonia…) - Poor prognosis	↓↓ ANC ($< 200/ mm^3$)
Chronic benign neutropenia (AD/AR)	Mild to moderate neutropenia	No ↑↑ risk of pyogenic infection	↓↓ ANC Normal TLC
Dyskeratosis congenital (AR)		Short stature, MR, pigmentation, Ectodermal dysplasia, Ocular	↓↓ ANC
Shwachmann-Diamond $ (AR)		Met. Chondrodysplasia, MR Pancreatic insufficiency Neutropenia	↓↓ ANC
Cartilage-hair$ (AR)		- Short-limb dwarfism - Hair: light, sparse - Immunodeficiency	↓↓ ANC X-ray Dysplasia
Chediak-Higashi $ (AR)	Defective Degranulation; • PNL • Melanocytes • Platelets	• ↓↓ ANC (giant PNL granules) • Partial albinism, light skin, silvery hair & photophobia. • Defective Platelet function (bleeding)	↓↓ ANC ↑↑ Bleeding time PLT functions
Hyper-IgM	Defective switch (IgM ⟶ IgG)	Recurrent bacterial infection	↓↓ ANC ↑↑ IgM ↓↓ IgG
GSD type Ib	↓↓ G 6 P translocase	Hepatomegaly, hypoglycemia, ↑↑ Uric acid, Cholesterol, Lactate	↓↓ ANC ↓↓ PNL function

Extrinsic disorders causing Neutropenia

1. **Infection***
   - Bacterial: Typhoid, TB, Tularemia (Francisella tularencis), Pertussis, Brucellosis, sepsis
   - Viral*: CMV, EBV, Viral hepatitis, VZ, MMR (Measles, Mumps, Rubella)
   - Fungal: Histoplasmosis
   - Protozoal: Malaria, Leishmaniasis
   - Rickettsial: Rocky Moutain spotted fever
2. **Immune:**[Anti-neutrophil Ab]
   - Autoimmune (analog to AIHA): usually in children with immunodeficiency
   - Immune neonatal neutropenia
     - Maternal autoantibodies (Transplacental passage of maternal Ab)
     - Alloimmune (analog to Rh incompatibility & NATP): Maternal Ab
3. **Irradiation**
4. **Drug-induced** *(3 mechanisms)*: Toxic, immune or idiosyncrasy
5. **Hypersplenism**
6. **BM infiltration**
7. **Nutritional (Folic, B_{12} or protein deficiency)**

Eosinophilia

Definition

Total WBC count 2 SD above the mean for age

Etiology

1. **Allergic** disorders: Bronchial asthma, atopy, rhinitis, urticaria, angioneurotic edema
2. **Infections**:
   - Trematodes: Schistosomiasis
   - Cestodes: Echinicoccus
   - Nematodes: Ascaris, Ankylostoma
   - Protozoa: Toxoplasmosis, Pneumocystis carinii, Malaria
   - Fungi: Aspergillosis

Omenn syndrome
- HSM & Lymphadenopathy
- Intractable diarrhea
- Exfoliative erythroderma
- Eosinophilia &↑↑ IgE

3. **Malignancy**: AML, eosinophilic leukemia, Hodgkin lymphoma
4. **Immunodeficiency**: Omenn syndrome, Wiskott-Aldrich, Hyper-IgE syndrome
5. **Vasculitis**
6. **GIT**: Eosinophilic gastroenteritis
7. **Histiocytosis**
8. **Tropical eosinophilia:** asthma-like symptoms + LN + eosinophilia
   Etiology: Helminthes [filaria*]
9. **Loeffler syndrome:** Mild respiratory symptoms + Pulmonary infiltrates + eosinophilia
   Etiology: Helminthes & Drugs
10. **Idiopathic hypereosinophilic $**
11. **Bronchiolitis obliterans**
12. **ARDS**

Idiopathic hypereosinophilic syndrome
Diagnostic criteria (Triad)
- Eosinophilia ≥ 1500/ mm^3 ≥ 6 months
- C/P of organ involvement
- No other diagnoses to explain

Clinical Picture:
1. Heart: Restrictive cardiomyopathy
2. Lungs: RD, Pulmonary infiltrates
3. HSM
4. Blood: anemia, thrombocytopenia, eosinophilia
5. Neurologic: Peripheral neuropathy

Prognosis: 75% mortality
Treatment: Steroids & Hydroxyurea

Hematopoietic Stem Cell Transplantation

Definition

It is infusion of stem cells into a recipient

Types

A) **Autologous transplantation** (from the same individual)

B) **Allogeneic transplantation** (from other compatible individuals)

1. **Bone marrow**
2. **Umbilical cord blood**
3. **Peripheral blood stem cells**

Indications

- ALL & AML
- Hodgkin & non-Hodgkin lymphoma
- Thalassemia & Sickle cell anemia
- Neuroblastoma & Wilms
- Aplastic anemia
- Fanconi anemia & Dyskeratosis congenita
- Diamond-Blackfan
- PNH
- Osteopetrosis
- Congenital platelet dysfunction
- Severe combined immunodeficiency
- Wiskott-Aldrich syndrome
- Omenn syndrome
- Leukocyte adhesion deficiency (LAD)
- Chronic granulomatous disease (CGD)
- Chediak-Higashi disease
- Hyper IgM syndrome
- Kostmann syndrome
- MPS
- Adrenoleukodystrophy

Preparation

☒ **Rationale**

a. Ablation of the patient's BM (either normal or abnormal)

b. Immunosuppression to allow engraftment (prevention of rejection)

c. Tumor therapy (in cases of malignancy)

☒ **Method**

a. High-dose chemotherapy [Cyclophosphamide, Busulfan, Cytarabine…]

b. ± Irradiation

Post-transplantation *(To prevent rejection & GVHD)*

Immunosuppressive drugs: Steroids (methylprenisolone), Cyclosporine, Methotrexate

Evidence of Engraftment

- BM cellularity
- Improved parameters (e.g., immunologic parameters in SCID…)
- Genetic study

SMZ-TMP: for pneumocystis carinii

Complications

1. Opportunistic infections: prophylactic % therapeutic antimicrobial
2. GVHD *(see immunology)*
3. Graft rejection & graft failure
4. Malignancy
5. HUS, TTP
6. Neurological manifestations due to cranial irradiation or drugs (cyclosporine)
7. Cataract
8. Growth retardation due to irradiation (hypopituitarism), drugs (steroids)
9. Hypothyroidism (primary or secondary)
10. Hypogonadism (primary)

Outcome Depends on 1ry etiology & frequency of previous transfusions [≈ 60-80%]

Generalized LN Enlargement

1. **Infections**
   a. **Bacterial:** Typhoid, TB, Brucellosis, sepsis
   b. **Viral:** EBV (infectious mononucleosis), CMV, Viral hepatitis, VZ
   c. **Protozoa:** Malaria, Leishmaniasis
   d. **Fungal:** Histoplasmosis
   e. **Rickettsial:** Rocky Moutain spotted fever
2. **Neoplastic**
   a. **Hematologic:** Leukemia, lymphoma (Hodgkin & non-Hodgkin)
   b. **Non-hematologic:** Neuroblastoma
3. **Immune**
   a. Collagen-vascular diseases: Systemic onset JRA & SLE
   b. Immunodeficiency: Chronic granulomatous disease & Chediak-Higashi disease
4. **Storage diseases**
   a. Gaucher
   b. Neimann-Pick
5. **Drug:** Phenytoin
6. **Miscellaneous:** Sarcoidosis, Hyperthyroidism (Graves Disease)

Cervical LN Enlargement

1. **Infection**
   a. **Bacterial:** Pharyngitis & tonsillitis
   b. **Viral:** URT infection, EBV (infectious mononucleosis), CMV, VZ
   c. **Mycobacteria:** TB & atypical mycobacteria (M. avium, intracellulare, kansaii, marinum)
   d. **Fungal:** Histoplasmosis
   e. **Protozoa:** Toxoplasmosis
   f. **Cat scratch disease:** Bartonella henselae
   g. **Tularemia:** Francisella tularencis
2. **Neoplastic:** Lymphoma, leukemia
3. **Immune:** Kawasaki disease
4. **Occipital LN:** Pediculosis, Rubella, scalp & ear infection
5. **Generalized Lymphadenopathy**

Cat-scratch disease:
- Red papule
- Regional LN
- FAHM
- Parinaud oculoglandular $

Investigations: ELISA, PCR
Rx: Azithromycin

Tularemia: (Zoonotic)
- Ticks, rabbits, rodents
- Red papule
- Regional LN
- FAHM
- Parinaud oculoglandular $

Investigations: ELISA, PCR
Rx: Gentamicin

Approach to a case of Lymphadenopathy

(A) History

(B) Physical examination

(C) Investigations

Indications of LN biopsy

- Persistent or unexplained fever, Weight loss, Night sweating
- Hard or fixed LN
- Associated supraclavicular or mediastinal LN
- ↑↑ Size > 2 wks
- Persistent > 12 wks

Graft Versus Host Disease

The most common cause of mobidity & mortality after allogeneic HSCT

Definition

- It is tissue damage caused by engraftment of **immunocompetent** donor's lymphocytes in an **immunocompromised** host with **histocompatibility** difference.
- GVHD usually follows HSCT or simple blood transfusion
- It may be beneficial in cases of graft versus leukemia (GVL)

Clinical Picture

		Acute GVHD	Chronic GVHD
Onset		7-60 days (< 100 days)	> 100 days
C/P	**Skin**	Erythematous rash	Sclerodermatous changes
	GIT	Secretory diarrhea	Malabsorption
	Liver	Hepatitis	Cholestasis

Prevention

1. Proper matching (Histocompatible donors)
2. Post-transplantation immunosuppressive drugs: Methotrexate, Cyclosporine, Steroids
3. Removal of T-cell from the grafts (monoclonal Ab or physical separation)
4. Use of irradiated blood

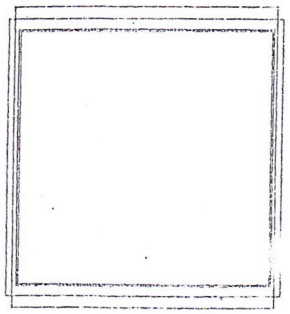
Treatment

Immunosuppressive drugs: Steroids (methylprenisolone), ATG

	Iron deficiency	β Thalassemia trait	Thalassemia Major	Lead poisoning	Chronic diseases
MCV	↓↓	↓↓	↓↓	↓↓	N or ↓↓
RDW	↑↑	N	↑↑	↑↑	N
HbA_2	N	↑↑	↑↑	N	N
Iron	↓↓	N	↑↑	N	↓↓
TIBC	↑↑	N	N	N	↓↓
Ferritin	↓↓	N	↑↑	N	↑↑

Medical-Surgical Nursing Department
Medical Unit

CLINICAL EVALUATION SHEET
Academic year 2012-2013



Student Name:..... Instructor's Name:.....

Clinical Experience:..... Duration:.....

Days of Being Late:..... Days of Absenteeism:.....

Comment:.....

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Clinical Score:..... Clinical Exam.....

Student Signature:..... Date:.....

Clinical Instructor Signature:.....